DOCUMENT RESUME

ED 248 012 PS 014 472

TITLE Center for Research for Mothers and Children: 1983 Progress Report.
INSTITUTION National Inst. of Child Health and Human Development (NIH), Bethesda, Md.
PUB DATE 83
NOTE 80p.
PUB TYPE Reports - Research/Technical (143) -- Reports - Descriptive (141)

EDRS PRICE MF01/PC04 Plus Postage.
DESCRIPTORS *Behavior; *Child Development; *Disabilities; Financial Support; Genetics; Learning; *Mental Retardation; Nutrition; Perinatal Influences; Pregnancy; *Research Projects
IDENTIFIERS *Center for Research for Mothers and Children; Developmental Disabilities; Endocrine System; Research Results; Research Summaries; Teratology

ABSTRACT

Described in this report are the extramural activities for fiscal year 1983 of the Center for Research for Mothers and Children (CRMC). The CRMC is designed to advance knowledge about fetal development, pregnancy, and birth; to identify the prerequisites of optimal growth and development through infancy, childhood, and adolescence; and to contribute to the prevention and treatment of mental retardation, developmental disabilities, and other problems of childhood and adolescence. The extramural activities of the Center are administered through three branches: the Clinical Nutrition and Early Development Branch (CNED), the Mental Retardation and Developmental Disabilities Branch (MRDD); and the Human Learning and Behavioral Branch (HLB). The largest branch in the CRMC, the CNED has three sections: a Genetics and Teratology Section, a Pregnancy and Perinatology Section, and a Nutrition and Endocrinology Section. In June of 1983 the CRMC provided more than $119 million in support of over 1,000 research and research training projects concerned with the special health problems of children, mothers, and families. Information concerning each branch and section includes an overview, descriptions of the unit(s) involved, a summary of program activities, a table disclosing National Institute of Child Health and Human Development grants and contracts active during June 1983, descriptions of research activities, and a brief report of staff activities. (RH)

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1983
Progress Report

Center for Research for Mothers and Children

National Institute of Child Health and Human Development

National Institute of Child Health
and Human Development

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Table of Contents

	PAGE
CENTER FOR RESEARCH FOR MOTHERS AND CHILDREN	
Office of the Director: Introduction	1
Workshops conducted in 1983	2
Research Highlights - All Branches	3
CLINICAL NUTRITION AND EARLY DEVELOPMENT BRANCH (CNED)	
Overview	9
GENETICS AND TERATOLOGY SECTION	
Program Activities	13
Emphasis Areas	13
Financial Support	14
Research Highlights	14
Developmental Genetics	14
Regulation of Gene Expression	14
Congenital Adrenal Hyperplasia	15
Developmental Biology	15
Early Embryo Development	15
Limb Development	15
Teratology	16
Epidemiology of Birth Defects	16
Neonatal Infections - Cytomegalovirus	16
Limb Malformations	16
Embryotoxic Agents - Phenytoin	17
Developmental Immunology	17
Ontogeny of Immunity	17
Immunology of Breast Milk	17
Staff Activities	18
PREGNANCY AND PERINATOLOGY SECTION	
Program Activities	21
Emphasis Areas	21
High Risk Pregnancies	21
Fetal Pathophysiology	21
Premature Birth and Labor	21
Disorders of the Newborn	21
The Sudden Infant Death Syndrome	22
Major Research Programs	22
Contract Program	22
Research Training	22
Financial Support	22
Research Highlights	23
Research Accomplishments of the Major Research Programs	23
Research Accomplishments under the Grants Program	24
High Risk Pregnancies	24
Fetal Pathophysiology	25
Premature Birth and Labor	26
Disorders of the Newborn	26
The Sudden Infant Death Syndrome	27
Conferences and Staff Activities	27

NUTRITION AND ENDOCRINOLOGY SECTION
Program Activities 30
Emphasis Areas 30
Contract Program 30
Research Training Program in Nutrition and Endocrinology 30
Financial Support 30
Research Highlights in Nutrition 31
Maternal-Fetal Nutrition 31
Infant Nutrition 31
Cultural, Behavioral, and Developmental Aspects of Food and Nutrition 32
Developmental Gastroenterology 33
Obesity and Nutritional Antecedents of Adult Disease 34
Research Highlights in Developmental Endocrinology 35
Treatment of Precocious Puberty with LHRH Analogue 35
Short Stature and Human Growth Hormone 35
Congenital Adrenal Hyperplasia 35
Genetics of Susceptibility to Insulin-Dependent Diabetes Mellitus (IDDM) 36
Research Highlights in Developmental Physiology 36
Staff Activities 36

MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES BRANCH (MRDD)
Overview 39
Program Activities 39
Financial Support 39
Research Training 40
Mental Retardation Research Centers (MRRC) 40
Research Highlights 42
Biomedical Research 42
Down Syndrome 42
Phenylketonuria (PKU) 43
Neural Tube Defects (NTD) 44
Krabbe's Disease (Globoid Cell Leukodystrophy) 44
Prematurity in Primates: Causes, Effects, Prevention 45
Behavioral and Social Sciences Research 45
Early Identification of Risk Infants 45
Perceptual and Attentional Processes 47
Learning and Cognition 47
Amelioration and Treatment of Retarded Children 49
Personality and Adaptation 50
Social Processes 51
Family Processes and Interaction 51
Language and Communication Processes 52
Behavior in Residential and Community Settings 52
Staff Activities
Forward Plan 53
Publications 53
Conferences and Workshops 53

HUMAN LEARNING AND BEHAVIOR BRANCH (HLB)
Program Activities 55
Financial Support 57
Research Highlights 57
Biological Basis of Behavioral Development 57
Behavior Genetics 57
Developmental Neurobiology 58
Developmental Behavioral Endocrinology 58
Learning and Cognitive Development 58
Early Learning in Animals 59
Visual Perception in Infants, Children and Adolescents 60
Cognitive Development 60
Social and Affective Development 61
Social Interaction in Children 61
Adolescence 61
The Family 61
Communicative Abilities 62
Comparative Animal Models 62
Research in Reading 63
Behavioral Pediatrics 63
Health Behavior 64
Illness Behavior 64
Risk Taking 64
Neonatal Behavior 65
Staff Activities 66

Center for Research for Mothers and Children

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INTRODUCTION

The Center for Research for Mothers and Children (CRMC), is one of the two extramural research support components of the National Institute of Child Health and Human Development. The CRMC stimulates, coordinates, and supports fundamental and clinical, biomedical and behavioral research and research training associated with normal human development from conception to maturity and those factors or special health problems which may delay or interfere with normal development. Thus, CRMC research for mothers, children, and families is designed to advance knowledge about fetal development, pregnancy and birth; to identify the prerequisites of optimal growth and development through infancy, childhood, and adolescence and to contribute to the prevention and treatment of mental retardation, developmental disabilities and other childhood and adolescent problems. The extramural activities of the Center are administered through three branches: the Clinical Nutrition and Early Development Branch, the Mental Retardation and Developmental Disabilities Branch and the Human Learning and Behavioral Branch.

The Clinical Nutrition and Early Development Branch focuses on the normal and abnormal biological development of the fetus and infant and on the effects of perinatal conditions and events on development. Of particular interest are sudden infant death syndrome (SIDS) and studies of drug action and disposition during pre and postnatal development. The Branch also supports research on the nutritional needs of pregnant women, fetuses and children and on the inter-relationships of nutrition, anthropology, and growth and development.

The Mental Retardation and Developmental Disabilities Branch focuses on research on the etiology, pathogeneris, epidemiology, diagnosis, treatment and prevention of retardation and related development disabilities, examining the biomedical, behavioral and social process involved. Emphasis is placed on the biologic basis of mental retardation with priority being given to the role of genetics. For example, such chromosomal defects as those causing the Down Syndrome and Fragile X Syndrome, the single gene defects of PKU and the polygenic origin of neural tube defects are studied.

The Human Learning and Behavioral Branch supports research on the development of human behavior from infancy through childhood and adolescence to early maturity. Studies are supported in developmental psychobiology, learning, cognitive and communicative processes, social and affective development, and health related behaviors as well as learning disabilities, dyslexia, and related language disorders. Of special interest are prenatal and perinatal influences (including drugs and environmental agents) on infant behavior and child development.

The activities of these three Branches during FY 1983 are summarized in this progress report. In June of 1983 the CRMC provided more than $119,000,000 in support of over 1,000 research and research training projects concerned with the special health problems of children, their mothers and families (see Table 1).

This represented approximately 57% of all monies distributed by the NICHD to laboratories, hospitals and research facilities throughout this country and abroad.

As part of its ongoing effort to encourage cross fertilization of the research activities of the major components of the CRMC, the Office of the Director, CRMC, has established an informal seminar series for all scientific staff which convenes periodically for "brown bag" luncheon meetings. The Office of the Director has also encouraged staff of all components of the Center to attend and participate in the conference/workshop programs supported by the CRMC. The following is a list of conferences and workshops held during FY 1983:

Workshop on the "Fragile X Syndrome"
25-26 April 1983 Bethesda, Maryland

Workshop on "Intrauterine Growth Retardation"
17-20 July 1983 Bethesda, Maryland

Conference on "Developmental Behavioral Pharmacology"
21-24 August 1983 Leesburg, Virginia

NICHD-NIADDK Workshop on "Morphogenesis and Malformations of the Skin"
22-23 September 1983 Bethesda, Maryland

Conference on "Research on Families of Retarded persons"
11-13 September 1983 University of North Carolina (Rougemont)

Conference on "Child Health Behavior": Research Status and Priorities in Behavioral Pediatrics"
11-14 September 1983 Leesburg, Virginia

Conference on "Developmental Genetics and Learning"
20-23 September 1983 Leesburg, Virginia

Dr. Sumner J. Yaffe, internationally renowned pediatrician and pharmacologist, continues to serve as the Director of the CRMC. In addition to full administrative and scientific responsibility for the activities of the Center, he has maintained a high degree of interest and expertise in his area of specilaization and is in much demand as a discussant and lecturer. For example, he was the keynote speaker at the Forth International Symposium on Pediatric Pharmacology in Dusseldolf, West Germany. His presentation was titled, "Problems of Drug Testing in Children in the United States".

Dr. James F. Kavanagh, Associate Director of the CRMC, has also had an opportunity to discuss research areas of interest to him. He gave the commencement address at West Chester State University, and participated in the Second World Congress on Dyslexia in Porta Carras (Halkidiki) Greece.

During the fiscal year the scientific staff of the CRMC have also participated in a wide variety of research meetings. These staff activities are included in Branch reports which follow.

Following are significant research highlights from the Center for Research for Mothers and Children:

Clinical Nutrition and Early Development Branch:
Genetics and Teratology Section

- One of the intervening sequences (intron B) of the rat growth hormone gene contains a strong RNA polymerase III promoter which allows the efficient transcription of this gene. Such a finding of a gene regulatory element in a non-coding portion of the genome such as an intron provides a significant new advance in our understanding of the regulation of function of genes.

- Foreign genes have been injected into the fertilized eggs of mice and have produced new mice that carry the introduced beta-globin genes in their germ line. This successful integration of functional genes into a host chromosome provides the basis for studies which now aim to determine the location and structure of regulatory genomic sequences adjacent to a coding gene that are involved in the erythroid cell-specific and stage-specific activation of the beta-globin genes.

- Because antibody is available for the enzyme responsible for the 20-22 desmolase form of congenital adrenal hyperplasia, good progress is expected in developing a cDNA probe as well as in identifying and characterizing the gene for this enzyme. The long range goal is to study cloned genomic DNA from selected patients with congenital adrenal hyperplasia in an effort to determine the exact genetic lesion in one or more of these diseases.

- NICHD-supported investigators study how the spacial heterogeneities of maternally produced cytoplasmic substances in the fertilized egg contribute to the regional generation of specific developmental potentials of subsequent embryonic cells. They address the question of which maternal compounds determine, for example, muscle cell lineages and activate muscle-specific genes or which play a role in the determination of the germ cell line. The characterization of some of these morphogenetic mRNAs and proteins is well underway.

- Limb development studies attempt to obtain a better understanding of how cells in the developing extremity are determined to later become muscle, cartilage, bone or connective tissue. They also include the establishment of limb patterns in the outgrowing extremity. Great advances are being made by NICHD-supported investigators in the study of cell and tissue interactions that are necessary for the development of specific parts of the limb.

- One NICHD epidemiologic study is specially designed to assess familial recurrence risks of pregnancy wastage in terms of fetal and perinatal deaths and congenital malformations. Factors associated with the outcome of pregnancy and survival of the infant will be evaluated. Sample sizes are sufficient for vigorous testing of hypotheses. These data will assist in developing a deeper understanding of the etiology of congenital malformations and will provide a basis for more precise reproductive counselling.

- Cytomegalovirus infections, which are the most common congenital infections in humans, lead to birth defects including mental retardation, epilepsy,

deafness, blindness, cerebral palsy and muscular deficiency. Transmission of cytomegalovirus (CMV) to embryos could be either through CMV associated with semen and the female genital tract during implantation, or by the transplacental route. These two routes of infection as well as the role played by the endometrium as a possible site of infection are being explored.

- Both clinical and basic biological studies on mutant limb development are supported in an attempt to gain a molecular understanding of the morphogenetic processes. The cell surface is recognized as a controlling factor in growth, differentiation and morphogenesis. Therefore important studies seek out variations in the surface membrane glycoproteins of mutant mesodermal cells as they differentiate into cartilage. Temporal changes in the biochemical characteristics of the cell surface membranes will be identified at distinct phases in chondrocyte differentiation.

- The drug, phenytoin, is widely used for the treatment of grand mal seizures. It is implicated in the causation of neural tube defects through folate deficiency and it is also embryotoxic. An NICHD-supported study is attempting to clarify the embryotoxic risks of folate deficiency induced by anticonvulsant drugs. The link between the two toxic effects, folate deficiency and embryotoxicity, has not been made. Therefore, biochemical mechanisms for how phenytoin causes folate deficiency will be pursued. These studies will increase our knowledge of the normal and abnormal metabolism of folates not only in the adult female but also in the developing animal.

Pregnancy and Perinatology Section

- Asymptomatic urinary tract infection is thought by some to contribute to preterm birth and fetal growth retardation. One perinatal microbiologist has found that maternal antibody to E.coli bacteria cross-reacts immunologically with antigen preparations of normal kidney, muscle, and placenta. Also, she found in a prospective study a significant association between the presence of maternal E.coli antibody in the urinary tract and the risk of low birth weight.

- A new technique has been developed in sheep allowing continuous visual observation of the fetus in-utero through a double wall plexiglass window in parallel with gathering of physiologic measurements. Preliminary observation of 68 fetuses videotaped in-utero for more than 300 hours did not show behavioral wakefulness during maternal resting activity.

- The fetus and newborn may compensate for hypotension by release of vasopressor substances so that the renin-angiotensin system appears to play a larger role than in adults. Hypotension may be a contributor to the oliguria seen in infants who are asphyxiated at birth.

- Researchers have successfully treated human newborns with respiratory distress syndrome by tracheal instillation of human-derived surfactant extracted from term amniotic fluid. Treatment of nine infants has shown an immediate improvement of respirator function and consequent oxygenation.

- A protein of fetal origin (present in fetal urine) may trigger the biochemical events leading to the onset of labor.

Nutrition and Endocrinology Section

- NICHD-supported investigators have produced sheep models of IUGR in order to assess the feasibility of intrauterine nutritional therapy delivered directly to the fetal stomach. Results show that infusion of a solution of glucose and amino acids during the period of maternal dietary restriction significantly increases birth weight and crown-rump length when compared to unsupplemented fetuses of nutritionally deprived ewes. This discovery may pave the way for the testing of intrauterine nutritional therapy in humans.

- Much has recently been learned about the complicated composition of human milk and how it reflects the metabolic needs of the newborn. Milk is not just a fluid containing nutrients. It is composed of a large array of constituents, many of which have important anti-microbial and other non-nutritive functions.

- The development of the child's conception of food follows a sequence. Children under three years seem willing to accept anything as food and will reject items only if they are distasteful. Gradually, rejection because of anticipated harm appears. Rejections as inappropriate or disgusting appear last. Rejection of foods because of contact with offensive substances, a hallmark of disgust, does not appear until at least age 6.

- Of great interest is that infantile obesity does not predict adult obesity. However, obesity in childhood after age four does predict obesity in adulthood. Obesity is not randomly distributed through the population. Rather, obesity falls along socioeconomic gradients and is most common in lower-income females and in median income males. Obesity also follows family line. With two obese parents the child has a 300% greater chance of becoming obese, and the child of two obese parents is, at adulthood, over 300% fatter than comparable children of two lean parents.

- Recently a promising treatment has been developed for idiopathic central precocious puberty. Many cases have been successfully treated with a synthetic analogue of luteinizing hormone releasing hormone (LHRH). The synthetic decapeptide, a superagonist of LHRH, is modified at positions 6 and 10 and has an increased affinity for pituitary LHRH receptors and a longer half-life than LHRH. Initial results are most encouraging in that patients' gonadotropin levels revert to undetectable levels, and their sexual characteristics regress to pre-pubertal status.

- The imminent availability of large quantities of biosynthetic human growth hormone (hGH) represents a great accomplishment in the annals of modern endocrinology. From 1958 until 1982 the only treatment available for growth-hormone-deficient children was hGH extracted from pituitaries removed from human cadavers.

- Short children with apparently normal hGH and normal somatomedin C will respond to the administration of exogenous hGH with accelerated linear growth. These discoveries will prove beneficial in the clinical management of short children in the near future.

- The discovery of linkage between the genes of the HLA locus and 21-hydroxylase has made it possible in affected families to predict which siblings

are carriers and which siblings are genetically unaffected. It has been established that the allele Bw47 is the one most commonly associated with classical 21-hydroxylase deficiency. This allele carries a relative risk of 15.4.

- Non-diabetic siblings who have an HLA type identical to that of their diabetic sibling run a risk of beoming diabetic 50 times greater than that of children from non-diabetic families. There is a diabetes-susceptibility locus in the HLA region of Chromosome 6 that exists in extremely tight linkage with HLA types D_3 and D_4.

Human Learning and Behavior Branch

- Chromosome 15 has been linked to a subtype of dyslexia.

- Research on brain sexual dimorphism has shown that male macaque monkeys have more dendritic material in the preoptic area of their brain than females.

- Maternal coordination of circadian rhythms has been shown in rats. The results indicate the existence of an entrainable circadian clock in the suprachiasmic nuclei during fetal development.

- In utero learning in rats has been extended to odor aversion. Conditioned rat fetuses show increased running time as pups, postnatally, in a maze when re-exposed to the negative conditioned stimulus (odor of apple juice).

- Two week old babies have been shown to imitate facial expressions of an adult.

- Researchers studying able readers and those who have difficulty reading found that disabled readers do not use letter clusters to analyze reading material.

- Branch supported researchers have pioneered in the development and field testing of biological markers (saliva thiocyanate, carbon monoxide and plasma cotinine) to corroborate self-reports of smoking in adolescents. Such work has helped set new standards of measurement of covert behavior.

- The glabella reflex (eyeblink) can be augmented by presenting an auditory stimulus concurrently with a tap to the head of a neonate. This finding has allowed the measurement of hearing in two day-old sleeping babies.

Mental Retardation and Developmental Disabilities Branch

- Although the number of babies born with Down syndrome has been decreasing for the past several years, an increasing proportion of women who are at high risk to give birth to babies with Down syndrome may soon reverse this trend.

- The "PKU gene" has been isolated and has been tentatively mapped on chromosome 12.

- Discontinuation of a special diet with restricted amounts of phenylalanine at the age of six years may be harmful to the development of children with PKU.

- Preliminary results suggest that the incidence of neural tube defects in hamsters, which has a spontaneous rate of 17 percent, can be reduced by folate supplementation prior to and during pregnancy.

- Researchers at two of the Mental Retardation Research Centers, Vanderbilt University and University of Kansas, have recently completed studies showing how to improve learning performance in retarded youngsters. They report that by modifying the material to be learned, retarded children can learn as well as normal children. One research team calls the revised material "considerate texts."

- Researchers at the University of North Carolina's Frank Porter Graham Child Development Center have devised a new assessment instrument to document retarded children's strengths and weaknesses. This instrument will aid in planning educational programs for handicapped preschool children.

- A research group at Vanderbilt University has found that by training either handicapped or normal children to initiate social interaction with handicapped children, the sociability of the handicapped children can be improved. Such interventions may facilitate normalization of handicapped youngsters efficiently.

- A team of language specialists at the University of Wisconsin have recently developed and tested a computerized method for analyzing language samples. This will allow researchers to score language samples quickly and efficiently and will facilitate diagnosis of many different types of language defects.

Table 1.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1983
CENTER FOR RESEARCH FOR MOTHERS AND CHILDREN

Funds (in thousands)

Branch/Section	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	1,010	119,482	880	108,644	749	75,093	58	30,667	73	2,883	100	6,134	30	4,704
Clinical Nutrition & Early Development	713	76,507	618	68,415	540	55,632	19	10,513	59	2,270	68	3,709	27	4,383
Genetics & Teratology	(304)	(29,562)	(267)	(27,349)	(231)	(24,942)	(3)	(1,154)	(33)	(1,253)	(37)	(2,213)	-	-
Pregnancy & Perinatology	(234)	(20,666)	(202)	(25,765)	(174)	(17,226)	(13)	(7,913)	(15)	(626)	(20)	(1,038)	(12)	(1,863)
Nutrition & Endocrinology	(175)	(18,279)	(149)	(15,301)	(135)	(13,463)	(3)	(1,446)	(11)	(392)	(11)	(458)	(15)	(2,520)
Mental Retardation & Developmental Disabilities	149	28,013	133	26,416	93	9,661	31	16,336	9	419	14	1,463	2	134
Human Learning & Behavior	148	14,961	129	13,812	114	9,800	8	3,819	5	194	18	961	1	187

Notes: 1) Excludes scientific evaluation grants.
2) The Minority Biomedical Support grants (S06) are included in the research projects.

Clinical Nutrition and Early Development Branch (CNED)

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OVERVIEW

The CNED Branch is the largest Branch in the CRMC. Support is provided for basic and clinical research utilizing grant or contract mechanisms as appropriate. Training for research careers is supported through both Institutional and Individual National Research Training Awards, and also through participation in pre-doctoral summer training and in the Minority Biomedical Research Support Program administered by DRR.

The CNED Branch contains the following three Sections:

Genetics and Teratology Section supports research into the underlying mechanisms controlling both normal and abnormal development, and is structured around the following areas: developmental genetics, developmental biology, teratology, and developmental immunology. Clinical as well as basic studies are emphasized. The goal of this program is to prevent, alleviate and treat birth defects with a special focus on the structural abnormalities.

Pregnancy and Perinatology Section supports research to advance knowledge on pregnancy and maternal health, fetal growth and maturation, and newborn well-being. Program goals take into account the interrelationships of specific health and developmental problems occurring in the prenatal, perinatal and infant periods of life, and the effects these events may have on the development and well-being of the child. Activities are organized around five maternal-infant health problem areas: high-risk pregnancy, fetal pathophysiology, premature labor and birth, disorders of the newborn, and the sudden infant death syndrome.

Nutrition and Endocrinology Section supports research and research training on the roles played by nutrients and hormones in development during fetal life, infancy, childhood, and adolescence. Program goals include the achievement of a better understanding of the relationships between nutritional and hormonal factors during normal growth and development as well as in growth retardation and developmental disorders of the endocrine system.

Table 2 summarizes the grant and contract programs for each of the three CNED Sections, giving the dollars and numbers of projects active in June 1983. Detailed reports of the accomplishments of each of the Sections are presented in the following pages.

Beginning in FY82 the CNED Branch began an indepth examination of research needs concerning intrauterine development. A series of workshops and conferences were planned to extend over several years. The first conference was held in September 1982 and focused on the early development

of the fetal limb. In FY83, two additional research workshops were sponsored by CNED. The Pregnancy and Perinatology Section joined with the Nutrition and Endocrinology Section to sponsor a research planning workshop on "Intrauterine Growth Retardation" in July 1983. The participants explored the causes, diagnosis, and treatment of IUGR and recommended research needs and opportunities for NICHD. The second workshop was held in September 1983. Entitled "Morphogenesis and Malformations of the Skin," it emphasized genetic and environmental factors affecting normal and abnormal skin development in utero with an ultimate goal being prenatal diagnosis of skin disorders. All of these workshops have been designed to guide future research emphases and to lead to Program Announcements in selected areas.

As an extention of the interest in intrauterine development, Branch staff have established close working relationships with an emerging group of clinical scientists concerned with intrauterine diagnosis and therapy. Several productive discussions have been held concerning current NICHD research in this area and the need for additional efforts. Staff are assisting in the formation of a new professional scientific society through which CNED will seek to strengthen the scientific foundation for this promising specialty. Two other areas which have commanded staff attention and interest have been the long term safety of ultrasound as a diagnostic tool in pregnancy and the factors contributing to neural tube defects in utero. Both interests are expected to expand in the next fiscal year.

One of the major factors contributing to the relatively high rates of perinatal morbidity and mortality in the US is the high rate of premature birth. During FY83 the Branch, working collaboratively with the Epidemiology and Biometry Research Program, has developed a protocol for a major clinical trial of the control of genitourinary infections during pregnancy as one means to decrease premature labor. This study is being done under contract. An unusual aspect of this project is the fact that it is jointly planned, funded, and managed with another Institute, NIAID.

Staff of the Branch increasingly are being called upon to serve on a wide range of task forces and work groups involving other Institutes of NIH, federal agencies, and professional organizations. These reflect the widening recognition of the expertise of the professional staff by their peers and colleagues. Details of the staff activities are given in the following section reports. In addition to these activities, the chief of the Branch, Dr. Merrill S. Read, currently serves as NIH representative to the DHHS Task Force on Maternal and Infant Nutrition and to the USDA/DHHS Nutrition Education Committee for Maternal and Child Health Publications. He represents NICHD on the Executive Committee of the USDA-Baylor Children's Nutrition Research Center in Houston. Throughout FY83, Dr. Read also was heavily involved as one of the three DHHS representatives to plan and conduct the nationwide USDA-DHHS Video-Teleconference on Maternal and Infant Nutrition. Held on April 7, 1983, the teleconference was viewed by 10,500 physicians and nutrition professionals. Finally, Dr. Read serves as Chairman of the Committee on Education and Training of the American Society for Clinical Nutrition.

The Branch is pleased that Dr. Jeanette Felix joined the Genetics and Teratology Section as an expert in developmental biology. During her two year tenure, Dr. Felix will evaluate CNED's present support in developmental biology and formulate recommendations for future research activities.

During the summer of 1983, the Branch benefited greatly from two summer students: Ms. Margaret Baer (a pre-medical student) and Mr. Joseph Kim (a first-year medical student). Both contributed significantly to the Branch's efforts to streamline and improve scientific management information systems.

Table 2.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1983
CLINICAL NUTRITION AND EARLY DEVELOPMENT BRANCH

Funds (in thousands)

Health Area	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	713	$76,307	618	$68,415	540	$55,632	19	$10,513	59	$2,270	60	$3,709	27	$4,383
Genetics and Teratology	304	29,562	267	27,349	231	24,942	3	1,154	33	1,253	37	2,213	-	-
Pregnancy and Perinatology	234	28,666	202	25,765	174	17,226	13	7,913	15	626	20	1,038	12	1,863
Nutrition and Endocrinology	175	18,279	149	15,301	135	13,463	3	1,446	11	392	11	458	15	2,520

Notes: 1) Excludes scientific evaluation grants.
2) The Minority Biomedical Support grants (S06) are included with the research projects.

NICHD-OPE-PAS
September 12, 1983
Revised

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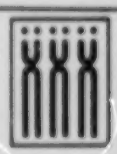

PROGRAM ACTIVITIES

Underlying the research program of the Genetics and Teratology Section is the concept that events very early in life can contribute to the life-long health and well-being of children and adults. This view avows that human development is a continuous process that begins with the maturation of male and female germ cells, is followed by fertilization, and continues through embryonic, fetal, and child development to yield the mature adult. However, maximum potential is not reached should disruptions in the process cause aberrations from the normal which result in developmental defects.

Three to seven per cent of children are afflicted with developmental defects at some time in their lives; for the great majority of these conditions the cause remains unknown. But with new technologies such as improved cell cultures, recombinant DNA, and monoclonal antibodies, basic biological and clinical studies can be better integrated to improve understanding of human developmental errors. New epidemiological models also allow more sophisticated data analysis.

Most congenital defects start during early development, perhaps as early as the egg or sperm. For this reason an ever increasing focus on studies of early embryo development is being fostered. The resulting developmental errors can be expressed as early death, spontaneous abortion, stillbirth, dysmorphology, growth disorders and/or post-natal developmental dysfunctions. The causes of congenital defects are multiple, but five etiologic categories are being explored in this research program: gene mutations, chromosomal aberrations, environmental agents, multifactorial causes and those of unknown origin. It should be noted that some malformations may not be due to genetic or external environmental factors, but may represent intrinsic errors of embryonic development.

Congenital defects represent a high priority research area within NICHD. They are broadly defined to include all the inborn structural, functional and biochemical defects found in the human organism which are initiated prior to birth or shortly thereafter, and which cause immediate or delayed abnormality. Structural defects are given special emphasis. Studies of both normal and abnormal limb development are identified as a highlighted research area for immediate attention.

Emphasis Areas

The Genetics and Teratology Section has been divided into four component research areas which complement each other, but which also contain some overlap so that the various activities must be viewed together as an overall effort. These areas comprise:

1. Developmental Genetics to determine the hereditary influences underlying developmental disorders and to understand hereditary instructions for the developmental process,
2. Developmental Biology to determine the mechanisms underlying normal human development against which aberrations of the process can be understood,

3. Teratology to assess adverse genetic and/or environmental influences on development, and to arrive at mechanisms by which developmental aberrations are produced, and
4. Developmental Immunology to understand maturation of the immune system as well as adverse pregnancy and early postnatal outcome produced as a consequence of immunologic responses or immaturity of the defense system.

Financial Support

As of June, 1983 the Genetics and Teratology Section funded a total of 304 research projects at the level of $29,562,000 (Table 1a). This included 18 Institutional National Research Service Awards and 19 Individual National Research Service Awards which represent $2,213,000 or 7.5% of the total research funds for this Section.

RESEARCH HIGHLIGHTS

Developmental Genetics

Research in developmental genetics includes human and clinical genetic studies as well as basic genetic approaches to increase our understanding of the role of genetic determinants in human development and inherited disease. The human studies include family investigations to determine inheritance patterns and genetic contributions to inherited disease, twin studies to separate genetic from maternal and external environmental contributions to developmental problems, and population studies to establish distributions and frequencies of abnormal genes. Clinical studies of specific genetic diseases investigate the phenotypic changes in relation to gene abnormalities and biochemical malfunctions. Basic genetic approaches attempt to identify specific genes involved in normal and abnormal developmental processes and to determine gene structure, function, and regulatory mechanisms governing gene action. Further included is the "switching" on and off of genes at specific developmental stages. Other studies are concerned with assignment of normal and disease genes to specific chromosomes or chromosomal loci. Two examples of such investigations are shown below.

Regulation of Gene Expression: Progress in genetics research is exemplified by NICHD-supported investigators who study the growth hormone gene. These investigators have found that one of the intervening sequences (intron B) of the rat growth hormone gene contains a strong RNA polymerase III promoter which allows the efficient transcription of this gene. Such a finding of a gene regulatory element in a non-coding portion of the genome such as an intron provides a significant new advance in our understanding of the regulation of function of genes. A further advancement is also afforded by the accomplishments of NICHD-supported investigators who have injected foreign genes into the fertilized eggs of mice and thus produced new mice that carry the introduced beta-globin genes in their germ line. This successful integration of functional genes into a host chromosome provides the basis for the investigators' studies which now aim to determine the location and structure of regulatory genomic sequences adjacent to a coding gene that are involved in the erythroid cell-specific and stage-specific activation of the beta-globin genes. Identification of the diverse gene regulatory elements (intron and flanking sequences)

will increase our understanding of the normal as well as abnormal expression of genes and ultimately allow us to devise a treatment for human genetic disease.

Congenital Adrenal Hyperplasia: The incidence of congenital adrenal hyperplasia is about one in every 5,000 births. These heritable disorders of steroidogenesis (cortisol, aldosterone and/or adrenal androgens) are due to impairments in the activity of various enzymes responsible for their synthesis. These steroids are responsible for carbohydrate, glycogen, and lipid metabolism, responses to stress, regulation of growth, metabolism of bone, modulating immune responses, fluid and electrolyte balance and development of secondary sexual characteristics. Therefore they are all vital to life with the exception of the androgens which influence sexual differentiation.

Using recombinant DNA technology, attempts are being made to understand the molecular bases of the various forms of congenital adrenal hyperplasia. Little is currently known about the enzyme defects underlying these diseases or about the genes responsible for these defective enzymes. Because antibody is available for the enzyme responsible for the 20-22 desmolase form of congenital adrenal hyperplasia, good progress is expected in developing a cDNA probe as well as in identifying and characterizing the gene for this enzyme. The long range goal is to study cloned genomic DNA from selected patients with congenital adrenal hyperplasia in an effort to determine the exact genetic lesion in one or more of these diseases. Information of this type would greatly increase our understanding of these diseases and may help in developing future therapies.

Developmental Biology

Studies in developmental biology are increasing our understanding of the mechanisms that underlie the development of various organ systems. These investigations range from the very early developmental period starting just after fertilization, during which the overall organization of the embryo is gradually established, to the later terminal maturation of the different body structures. Some studies reach into the postnatal period. The two examples that follow illustrate this.

Early Embryo Development: Current aspects of investigations which address early embryonic development are the uneven distribution of maternally produced cytoplasmic substances in the fertilized egg. NICHD-supported investigators study how the spacial heterogeneities of these molecules contribute to the regional generation of specific developmental potentials of subsequent embryonic cells. They address the question of which maternal compounds determine, for example, muscle cell lineages and activate muscle-specific genes or which play a role in the determination of the germ cell line. The characterization of some of these morphogenetic mRNAs and proteins is well underway. In the near future, application of the recombinant DNA technology should aid studies of gene activity during this developmental stage.

Limb Development: Studies of specific organ systems include the development of such structures as the limb. Limb development studies attempt to obtain a better understanding of how cells in the developing extremity are determined to later become muscle, cartilage, bone, or connective tissue. They also include the establishment of limb patterns in the outgrowing extremity. Great advances

are being made by NICHD-supported investigators in the study of cell and tissue interactions that are necessary for the development of specific parts of the limb. This is exemplified by the finding that mesenchymal cells can stimulate each other so that developmentally more advanced mesenchyme cells undergo chondrogenesis in the limb. It is also evident from established observations that the mesoderm must interact with the apical ectodermal ridge (AER) to produce outgrowth of the limbs. In the coming year, a start will hopefully be made in the development of monoclonal antibodies that can be used to identify the cell surface components as well as extracellular matrix constituents that mediate the cell and tissue interactions which are necessary for the differentiation of this organ system.

Teratology

Studies in teratology are directed to the causes of aberrant development result in congenital defects. A mutant gene or chromosomal aberration, an environmental chemical or physical factor, a maternal metabolic disease, or infection are all potential etiologic factors. Investigations focus on clinical medicine, biochemical and molecular genetics, cellular and molecular biology, epidemiology, reproductive biology, and developmental pharmacology and toxicology. Several ongoing studies in teratology follow.

Epidemiology of Birth Defects: A major research approach to teratology utilizes epidemiologic methods to study pregnancy outcome. One such NICHD study is specially designed to assess familial recurrence risks of pregnancy wastage in terms of fetal and perinatal deaths and congenital malformations. Factors associated with the outcome of pregnancy and survival of the infant will be evaluated. Sample sizes are sufficient for vigorous testing of hypotheses. These data will assist in developing a deeper understanding of the etiology of congenital malformations and will provide a basis for more precise reproductive counselling.

Neonatal Infections-Cytomegalovirus: Specific infectious agents are also undergoing in-depth study as causes of developmental errors. For example, cytomegalovirus infections, which are the most common congenital infections in humans, lead to birth defects including mental retardation, epilepsy, deafness, blindness, cerebral palsy and muscular deficiency. Transmission of cytomegalovirus (CMV) to embryos could be either through CMV associated with semen and the female genital tract during implantation, or by the transplacental route. These two routes of infection as well as the role played by the endometrium as a possible site of infection are being explored. Other studies are characterizing the pathology caused to the fetus by such infections. The stages at which placentas, embryos and fetuses are susceptible to infection will be determined. These investigations will contribute an understanding of the process by which CMV infections during early pregnancy induce embryonic death or abnormal development.

Limb Malformations: A new research focus within the Genetics and Teratology Section is the study of limb deformities insofar as they may be induced by genetic and environmental factors. Both clinical and basic biological studies on mutant limb development are supported in an attempt to gain a molecular understanding of the morphogenetic processes. The cell surface is recognized as a controlling factor in growth, differentiation and morphogenesis. There-

fore important studies seek out variations in the surface membrane glycoproteins of mutant mesodermal cells as they differentiate into cartilage. Temporal changes in the biochemical characteristics of the cell surface membranes will be identified at distinct phases in chondrocyte differentiation. These studies promise to be productive and will be pursued further.

Embryotoxic Agents - Phenytoin: The drug, phenytoin, is widely used for the treatment of grand mal seizures. It is implicated in the causation of neural tube defects through folate deficiency and it is also embryotoxic. An NICHD-supported study is attempting to clarify the embryotoxic risks of folate deficiency induced by anticonvulsant drugs. The link between the two toxic effects, folate deficiency and embryotoxicity, has not been made. Therefore, biochemical mechanisms for how phenytoin causes folate deficiency will be pursued. These studies will increase our knowledge of the normal and abnormal metabolism of folates not only in the adult female but also in the developing animal. The investigators will also attempt to modulate the embryotoxicity of phenytoin and of other anticonvulsant drugs with compounds which restore folate metabolism to normal.

Developmental Immunology

Studies in developmental immunology are closely related to studies of congenital defects. Five research categories are pursued. Studies of the ontogeny of immunity seek errors in maturation that lead to mild as well as severe immune deficiency states in man. Other investigations evaluate decreased immunologic competence associated with malnutrition in infants. An NICHD conference on Trace Element Regulation of Immunity and Infection was held in September 1981 and should provide the stimulus for new studies in nutritional immunology. The immunology of breast milk is being investigated since current studies suggest that ingestion of colostrum and milk may contribute protective anti-infectious components to the newborn. Another category includes studies of neonatal infections which focus on immaturity and developmental deficiencies in body defenses associated with specific types of organisms. Studies in reproductive immunology look for maternal-fetal immunologic mechanisms that protect the fetus from a potentially harmful maternal immunologic environment. Among these research categories ontogeny of immunity and immunology of breast milk are highlighted below:

Ontogeny of Immunity: This research is providing a breadth of knowledge of immunologic function using human and animal models. Vulnerability in host defenses due to the infant's genetic make-up and environmental influences, at specific periods during maturation, is the primary focus. A major goal is to identify the errors in maturation that lead to mild as well as severe immune deficiency states in man. In addition, studies of the wide variety of mechanisms that the human infant employs to protect itself from exogenous noxious agents will provide knowledge of responses to replicating material such as viruses and bacteria as well as environmental chemicals and drugs. Similar but more primitive humoral and cellular mechanisms are used for host defense in phylogenetically lower animals, and therefore evolutionary studies also have been useful in expanding knowledge on immunologic function in man.

Immunology of Breast Milk: The mammalian fetus is immunologically competent for many responses before birth, even though its immunologic defenses have not

yet been challenged. Nevertheless temporary immune protection is needed until the newborn immune system can react and develop a satisfactory response. Late in gestation, the developing fetus acquires passive immunity from maternal antibodies which are transferred from the mother to the fetus; this provides temporary humoral immunity. Since the human newborn is essentially devoid of functional secretory antibody at the intestinal mucosal surface, recent evidence suggests that ingestion of colostrum and milk may contribute passively to immune exclusion of infectious agents and other antigens. This becomes important since newborn sepsis is often associated with invasion of the infectious agent through the immature gastrointestinal tract. Numerous studies in newborns of many species indicate that maternal milk provides protection against such infection. In some species such protection may even be necessary for survival. Current information points to the importance of the antibodies and leukocytes in the breast milk. In fact, it is now well established that colostrum and milk from most mammals are essentially suspensions of viable cells in a highly nutritive medium that is rich in immunoglobulins (antibodies).

It remains to be determined specifically how breast milk might provide immunologic protection following ingestion during the newborn period. Some of these investigations focus on what effects the antibodies, antigens, and possible immune complexes in colostrum might have on the subsequent immune responsiveness of the nursing neonate. Other studies are now being extended to determine the effect of gut associated lymphocyte production of secretory antibody in newborns. Other studies will examine the mechanisms by which colostrum provides passive protection against antigen uptake and enterotoxin/bacterial binding to the neonatal gut surface. Still other studies are pursuing the possible harmful effects of bacteria and viruses carried by breast milk, reactions to allergens ingested by the mother and transmitted in milk, graft-versus-host disease, autoimmune disorders, and passage of environmental contaminants and drugs. Continued support of these efforts will provide answers to the protective potentials of breast milk. The biological significance is promising and must be clarified.

STAFF ACTIVITIES

Section staff participate in various trans-NIH activities and joint efforts with other government agencies. Dr. Delbert Dayton, Section Chief, is a member of the NIH Coordinating Committee For Blood-Related Activities and of a working group on Blood and Its Substitutes established by the Interagency Technical Committee on Heart, Blood Vessel, Lung and Blood Resources. He has also been appointed to the NIH Cystic Fibrosis Coordinating Committee which functions to stimulate and plan for research activities across NIH. Current planning by this committee includes input from NIH intramural scientists to develop a joint research agenda for NIH. Dr. Dayton represents NICHD on the NIH Working Group For Reye Syndrome which facilitates coordination of research efforts on this important health problem of children. A jointly sponsored NIH Announcement has been published and has been helpful in developing new research applications to strengthen efforts to study this disease. In addition Dr. Dayton serves as a member of the Public Health Service Reye Syndrome Task Force which has developed a protocol for a case-control study of the association between Reye Syndrome and salicylate intake. A committee organized by the Institute of Medicine of the National Academy of Science will act as an advisory body to the Task Force.

These studies are to be carried out through the assistance of State Health Departments. They are planned for initiation in the fall of 1983.

During this fiscal year Dr. Dayton also served on the planning committee of the Fogarty International Center for the development of an International Symposium on Poliomyelitis Control which was held in March, 1983. He served as rapporteur for the session on Strategies for Control at that meeting. Dr. Dayton and Mrs. Anne Krey serve on the PHS Steering Committee on Bioeffects of Ultrasound. Their charge is to develop a research agenda focusing on potential effects of diagnostic ultrasound on the developing organism. Dr. Dayton was made chairperson of a Subcommittee on Developmental Studies and Mrs. Krey serves with him in this activity. This group has planned a workshop with outside consultants who will meet in September 1983 to produce a report which will form the basis of a research agenda for future studies.

Section staff also organized and held a conference on Morphogenesis and Malformations of the Skin to formulate future research needs and to better integrate clinical studies with the most recent basic research advances. The most current areas of skin development research were presented at that meeting. As a direct result of the NICHD conference on Trace Element Regulation of Immunity and Infection, a "Nutritional Immunology Club" was organized and began holding annual gatherings at the time of the meetings of the Federation of American Societies for Experimental Biology. Two annual gatherings have now taken place and this is expected to improve information exchange and foster collaborative research activities.

Table 2a.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1983
GENETICS AND TERATOLOGY SECTION

Funds (in thousands)

Health Area	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	304	29,562	267	27,349	231	24,942	3	1,154	33	1,253	37	2,213	-	-
Clinical Genetics	24	3,152	23	3,132	17	2,216	2	753	4	163	1	20	-	-
Basic Developmental Genetics	57	5,639	51	5,496	37	4,588	1	401	13	507	6	143	-	-
Early Embryonic Development	98	9,473	82	8,033	70	7,598	-	-	12	435	16	1,440	-	-
CNS Development	18	1,356	15	1,304	15	1,304	-	-	-	-	3	52	-	-
Limb Bud Development	4	206	2	171	2	171	-	-	-	-	2	35	-	-
Chondrogenesis	6	716	6	716	6	716	-	-	-	-	-	-	-	-
Myogenesis	16	1,502	13	1,449	11	1,380	-	-	2	69	3	53	-	-
Teratology-Biological Causes	9	1,331	7	1,086	7	1,086	-	-	-	-	2	246	-	-
Teratology-Physical & Chemical Causes	19	1,691	18	1,633	18	1,633	-	-	-	-	1	58	-	-
Ontogeny of Immunity	16	1,407	14	1,284	13	1,246	-	-	1	38	2	123	-	-
Neonatal Infection	14	941	13	898	12	858	-	-	1	40	1	43	-	-
Immunology of Breast Milk	7	556	7	556	7	556	-	-	-	-	-	-	-	-
Reproductive Immunology	16	1,592	16	1,592	16	1,592	-	-	-	-	-	-	-	-

Notes: 1) Excludes scientific evaluation grants.
2) The Minority Biomedical Support grant (S06) are included with the research projects.

NICHD-OPE-PAS
July 8, 1983

Pregnancy and Perinatology Section

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PROGRAM ACTIVITIES

Emphasis Areas

Activities of the Pregnancy and Perinatology Section are organized around five maternal-infant emphasis areas.

1. High Risk Pregnancies: Over the last 20 years significant progress has occurred in maternal survival and well-being which has surpassed improvements in fetal outcome. Research efforts on high risk pregnancy are directed towards the closure of this gap while continuing studies in both normal and abnormal pregnancies. Special attention is being focused on placental function, the maintenance of pregnancy, maternal-fetal pharmacology, maternal exercise during pregnancy, and the special problems of the pregnant adolescent.

2. Fetal Pathophysiology: Studies in fetal pathophysiology are examining the factors influencing normal and abnormal embryonic development. Efforts focus on normal and abnormal development at the molecular, tissue, and organ levels. Emphasis is placed on studies facilitating the assessment of fetal status to provide meaningful antenatal diagnosis. Another area of special interest examines the mechanisms responsible for intrauterine growth retardation and its consequent increased morbidity and mortality.

3. Premature Birth and Labor: Premature labor and birth is a major cause of neonatal mortality and morbidity. Two-thirds of all infant mortality occurs among infants weighing 2500 grams or less at birth. Furthermore, the nation's high prematurity rate is responsible for our relatively poor performance in infant mortality compared to other countries. Consequently, this program supports studies of the normal onset of labor, why labor sometimes begins prematurely, and how premature labor might be stopped without detrimental effects. Also, interest is directed to the recognition of indicators of impending labor.

4. Disorders of the Newborn: Disorders of the newborn are responsible for approximately three-fourths of the infant deaths in the United States, and produce long-term disability for many individuals who are affected by them and survive. Research directed toward reducing the impact of these disorders includes studies of maternal health problems that affect the status of the infant, adaptation of the newborn infant to its environment, and problems in the early weeks of life that influence subsequent development and behavior.

5. The Sudden Infant Death Syndrome: The NICHD has made particular efforts to encourage research on the sudden infant death syndrome (SIDS) since 1974. Research to date has demonstrated that the SIDS infant no longer can be viewed as having been perfectly healthy prior to death, but rather is believed to have had developmental abnormalities. This revised concept suggests that a risk profile for SIDS could be developed and prevention efforts targeted to a high risk population. Current research efforts are evaluating these risk factors, identifying the cause(s) of SIDS, and improving methods for helping families cope with a SIDS death.

Major Research Programs

As a focal adjunct to research projects in the above five areas, NICHD has established Major Research Programs (MRPs) to provide an integrated approach to major unresolved problems in perinatal medicine. These MRPs support multidisciplinary research in areas where knowledge gaps have not been sufficiently addressed by ongoing research or where promising areas are in need of special stimulation. The Section supports six MRPs; four are in the area of diabetic pregnancies, one in prematurity, and one in fetal hypoxia.

Contract Program

The Section's contract program, though small in numbers, compliments the grant program and meets special needs in perinatal research.

In 1969 NICHD recognized a growing awareness of the potential for non-human primates in perinatal and developmental research. A special breeding colony was established in 1971 under contract at Davis, California, to provide Rhesus monkeys of known medical, reproductive and geneological history to NICHD-supported investigators in the United States. The colony specializes in dated pregnancies. Under the ongoing contract, 80-100 pregnant females are provided per year.

In September, 1983, the Section will initiate a contract-supported multi-center controlled clinical trial directed towards prevention of pre-term birth. The objectives of this are to identify specific types of maternal genito-urinary infection which are significantly associated with preterm labor and birth, and to test whether appropriate antimicrobial therapy of such infections can reduce the preterm birth rate in women at risk. This project has been developed in collaboration with NIAID with the assistance also of staff from the Epidemiology and Biometry Branch of NICHD.

Research Training

As of June, 1983 the Section funded 13 institutional Research Service Awards (NRSAs). One was in the the area of high risk pregnancy, two in fetal pathophysiology and 10 in disorders of the newborn. They supported a total of 6 predoctoral and 46 postdoctoral trainees. The predoctoral ones were in the biochemistry of pregnancy and developmental biology. The greatest number of postdoctoral trainees were in the area of neonatology. The Section also funded individual NRSAs. Four fellows were working in the high-risk pregnancy area examining various aspects of maternal and fetal

metabolism and placental physiology, one fellow in fetal pathophysiology, and two in disorders of the newborn studying neonatal infections and development of renal function respectively.

Financial Support

As may be seen in Table 1b, the Pregnancy and Perinatology Section supported 234 research grants and contracts as of June, 1983 amounting to $28.7 million. Included here were $4.6 million for the six MRPs. The Section holdings amounted to approximately 24% of the research and 16.9% of the research training supported by the Center for Research for Mothers and Children.

RESEARCH HIGHLIGHTS

Research Accomplishments of the MRPs

Four MRPs are in the area of "Diabetic Pregnancy," a major problem for mothers and children. Maternal morbidity is higher in diabetics, and although fetal mortality in diabetic pregnancy has been reduced, it is still higher than in the general population. Congenital anomalies, macrosomia, late intrauterine death and respiratory distress syndrome (RDS) remain significant problems. Investigators in these MRPs are attempting to clarify the pathophysiology of maternal metabolic disorders causing changes in the intrauterine environment which are unfavorable for the developing fetus.

In normal and conventionally managed diabetic patients the evaluation of fetal active and quiet periods has shown no difference at 28-32 weeks gestation. However, at 36-40 weeks gestation the fetus of the diabetic mother exhibits patterns of behavior resembling those in the younger normal fetus. This suggests that diabetes delays development of this particular aspect of brain mediated activity.

Other important studies have clarified the concept that although maternal insulin does not cross the placenta, it affects the quantity and quality of fuels available to the fetus during periods of intensive growth. Several studies have concentrated on gestational diabetes mellitus (GDM) characterized by glucose intolerance beginning during pregnancy. Comparisons between birthweight in offspring of mothers with GDM and mothers with normal carbohydrate metabolism show that the GDM group has heavier offspring. Also during the third trimester, GDM mothers have increased plasma values of glucose, free fatty acids and triglycerides. Birthweight of offspring appears to correlate with antepartum maternal plasma levels of some neutral amino acids, glucose and triglycerides. Measurements of amniotic fluid insulin (which is of fetal origin) also correlate with ultrasonographic indices of macrosomia. Many other studies are being carried out which will help understand the problems and delineate appropriate care for diabetic pregnancies.

The MRP dealing with fetal hypoxia addresses the question of maternal health problems associated with smoking and resultant fetal distress that may involve hypoxia leading to neurological deficit and/or intrauterine growth

retardation. Parallel studies on fetal hypoxia are being performed with humans and baboons. One hundred forty-four pregnant women enrolled in the study have delivered; comparison with appropriate non-smoking controls reaffirms that offspring of smoking mothers have a lesser birthweight (mean difference 444 grams). Fetal breathing activity recorded immediately after maternal smoking shows that it is not suppressed. These results stand in opposition to prior observations obtained with less quantitative techniques which reported inhibition of fetal breathing movements with smoking.

Studies carried out in pregnant baboons have shown that maternal agitation and pain may reduce uterine blood flow leading to decrease of fetal heart rate and oxygenation. These changes can be partially prevented by drug administration. Other studies by the same group of researchers are testing the hypothesis that measuring the concentration of neuropeptides in amniotic fluid may serve as a marker of fetal hypoxia.

Studies on human placental structure associated with smoking are ongoing. Results available on a limited sample have not revealed a specific lesion associated with smoking. However, placentas from smokers appear to contain more cadmium, with an amount proportional to the level of smoking. In a rat model exposure to cigarette smoke was shown to decrease the birthweight of offspring; their lungs were proportionally smaller than other organs.

The MRP studying initiation of parturition continues to examine the biochemical communication system involving gestational compartments that can set in motion events leading to human parturition. The importance of prostaglandins (PG) in this process is well recognized. After measuring PG concentrations in various biologic fluids, these researchers have determined intrauterine sources of biosynthesis and hormonal factors that stimulate rates of production. Presently they are examining the possibility that inhibition of PG biosynthesis by endogenous factors may be an important regulatory mechanism. The identification of a trigger or signal initiating the biochemical events leading to the onset of labor is the objective of other studies in this MRP. Fetal membranes and decidua seem to be poised for the receipt of a signal to initiate a series of biochemical steps leading to an increased biosynthsis of PG. A protein of fetal origin present in fetal urine was isolated and shown to induce PG formation in cultured amnion cells. It is possible to speculate that excretion of this protein into amniotic fluid could be a fetal signal to initiate parturition.

Research Accomplishments under the Grants Program

Selected scientific accomplishments during FY 83 pertinent to the Section's five problem areas are highlighted in the following paragraphs.

High Risk Pregnancies: Urinary tract infection (UTI) is a common complication of pregnancy. Symptomatic kidney infection, the most serious type of UTI, is associated with the higher risk of preterm labor. Asymptomatic UTI is thought by some to contribute to preterm birth and fetal growth retardation. One perinatal microbiologist has found that maternal antibody to E.coli bacteria cross-reacts immunologically with antigen preparations of normal kidney, muscle, and placenta. Also, she found in a prospective study a significant association between the presence of maternal

E.coli antibody in the urinary tract and the risk of low birth weight. Her studies are pursuing the hypothesis that maternal antibody may produce intrauterine growth retardation.

The most common cause of intrauterine infection in humans throughout the world is the cytomegaloviruses (CMV). At an incidence of one percent about 3,000 infants become severely handicapped in the U.S. annually, and another 3,000 will develop significant hearing and mental deficits. One investigator is studying CMV infections longitudinally in order to understand mechanisms of perinatal transmission, the effects of various forms of CMV infection, and the role of immunity in both mother and child. Contrary to other perinatal infections, recurrent maternal CMV infections are a frequent cause of intrauterine transmission of virus in man. These studies will clarify the natural history of the disease and indicate if a scientific basis exists for the development of a vaccine.

The antenatal detection of intrauterine growth retardation is necessary so that early management of this pregnancy complication may minimize the risk for perinatal asphyxia. Antenatal detection of IUGR on the basis of clinical data alone has limited potential. One investigator is examining the possible utility of amniotic fluid phospholipids to differentiate the small growth-retarded fetus (IUGR) from the one which is small on the basis of short gestation. Results suggest that phosphatidylglycerol was the only phospholipid which could predict subsequent IUGR infants. This information, in addition to an ultrasound examination, permitted a correct diagnosis in half of the patients.

Fetal Pathophysiology: Fetal growth is thought to be determined by many factors, such as maternal and fetal genetics, placental function, and environmental factors. However, there is little understanding of the mechanisms by which fetal growth is influenced by such factors. Specific fetal growth factors, such as epidermal growth factor (EGF) and nerve growth factor (NGF), have stimulating effects on specific fetal cell types. General somatic growth appears to be associated with the somatomedins, a family of peptide hormones. Intensive efforts are underway to purify certain somatomedins, develop assay techniques, and characterize their biologic effects.

Studies on fetal growth are balanced by research dealing with the functional maturation of fetal organs and systems. Presently knowledge of fetal physiology is very important as progressively younger and smaller newborns are becoming candidates for therapy. If surgical therapies are applied to fetuses in utero for correctable congenital lesions, their success will depend on clinical estimates of functional status and on post operative medical management. For this purpose one investigator is studying the hemodynamics and function of the fetal lamb kidney in the last trimester of pregnancy. Factors influencing renal function and fetal responses to stress are being analyzed.

Studies of fetal physiology aim to clarify the mechanisms regulating fetal breathing and the effects caused by wakefulness and hypoxia. A new technique has been developed in sheep allowing continuous visual observation

of the fetus in-utero through a double wall plexiglass window in parallel with gathering of physiologic measurements. Preliminary observation of 68 fetuses videotaped in utero for more than 300 hours did not show behavioral wakefulness during maternal resting activity. Administration of drugs causing increased breathing activity did not wake up the fetus. These studies are being expanded into the last 10 days of gestation when wakefulness is more likely to occur.

Current studies in lambs are examining the mechanisms of adaptation of the fetus to maintain homeostasis in the presence of chronic intrauterine hypoxia. The normal fetus and newborn were as capable as the adult animal of disposing of circulating catecholamines. Moderate maternal hypotension had very little effect on fetal blood pressure, heart rate, acid-base indices, or renal function but caused significant rise in fetal vasopressin, catecholamines and plasma renin activity. Therefore, the fetus and the newborn may compensate for hypotension by release of vasopressor substances so that the renin-angiotensin system appears to play a larger role than in adults. Hypotension caused a fall in urine flow and glomerular filtration rate and a rise in urine osmolality, suggesting that hypotension may be a contributor to the oliguria seen in infants who are asphyxiated at birth.

Premature Birth and Labor: The family of peptide hormones known as relaxin has been investigated for its growth-regulating properties. Animal data showed that relaxin may play a role in uterine quiescence during pregnancy, and, by means of its withdrawal, in the initiation of parturition. In addition, relaxin has profound effects on connective tissue, particularly on the uterine cervix which may also be important in parturition. In fact, preliminary clinical studies in humans have shown that relaxin causes cervical dilation. One investigator has been identifying the chemical structure of the relaxin group, and its corresponding DNA. Another investigator is analyzing the molecular biology of uterine relaxing factors, including relaxin. The biochemical effects are being correlated with their physical effects on the uterus. Ultimately, improved agents for the suppression of undesired preterm uterine contractions and premature birth may emerge from these fundamental investigations.

Disorders of the Newborn: The problem of fetal hypoxia and its possible short and long-term consequences continues to be an important area of research. Lambs studied at various postnatal ages have exhibited decreased oxygen transport at each successively lower inspired oxygen concentration. It was shown that below a certain level of oxygen transport (20 ml/kg/min.) oxygen consumption also diminishes with evidence of tissue hypoxia even though arterial pH does not fall. Lambs of 2 to 4 weeks postnatal age appear to have much less reserve for decreasing oxygen transport, probably as a function of their low resting arterial oxygen content due to postnatal anemia. These studies are helping to clarify the proportion of resting oxygen consumption in the newborn that is essential for metabolic activity and that part which is facultative and can be reduced without immediate tissue hypoxia.

Respiratory distress syndrome (RDS) continues to be an important problem during neonatal life. A group of investigators are characterizing the

subcellular metabolism of surfactant from synthesis to secretion and the subsequent reutilization of surfactant components by the type II pneumocyte. It has become evident that reutilization is the quantitatively dominant pathway and that there is some selectivity for certain phospholipids. However, a separate mechanism appears to influence the taking up of precursors by the alveolar surface of the type II cells. Other researchers have successfully treated human newborns with RDS by tracheal instillation of human-derived surfactant extracted from term amniotic fluid. Treatment of nine infants has shown an immediate improvement of respiratory function and consequent oxygenation. Repeat instillation of surfactant was needed in only one patient, and all continued to improve with supportive therapies.

The Sudden Infant Death Syndrome (SIDS): Studies of SIDS are exploring the mechanical properties of the human upper airway which in deceased infants was shown to collapse easily either by negative pressure or by neck flexion. During episodes of obstructive apnea, a similar pattern of sphincter-like closure was detected. It was shown in anesthetized rabbits that their "strap muscles" (sternothyroid and sternohyoid) have a phasic respiratory activity which helps in stabilizing the airway making it resistant to collapse. Parallel studies carried out in patients with Pierre Robin syndrome showed that brief face mask occlusion (loading test) resulted in the inspiratory closure of their airway. Further refinement of this test may facilitate the detection of risk to develop severe obstructive apnea. Other researchers are studying the hypothesis that interventions which tend to eliminate apnea also tend to reduce the amplitude of oscillatory breathing patterns. Breathing patterns and apnea are related in term infants, and in premature infants. It was shown that length of apnea increases with specific changes in the respiratory patterns. Therefore, apneas are not random nor isolated events. Research studies also are examining the role of endorphins in the maturation of ventilatory and cardiovascular functions during sleep and wakefulness under normoxic and hypoxic conditions. Following the recognition that opiate receptors are not uniform but of several subtypes, these are being tested in dogs with appropriate agonists. Preliminary results have shown that the mu and delta subtypes have different ventilatory functions. Their cardiovascular functions are being examined in similar fashion.

Another area of research is examining the possible link between botulism and SIDS. Infant botulism is emerging as a world-wide disease. Preliminary results show that 10-20% of SIDS victims in California and in Switzerland have a botulinum positive reaction in serum. Further refinement of laboratory methodology is underway to clarify possible relationships to specific botulinum type.

Conferences and Staff Activities

The Section provided partial support for the Perinatal Research Society's Annual Conference in 1983.

In July, 1983, the Section, in conjunction with the Nutrition and Endocrinology Section, held a Research Planning Workshop on Intrauterine Growth Retardation. The participants reviewed what is known about the epidemiology, causes, diagnosis and treatment of this condition. They

identified information that is needed and articulated directions for future research. It is planned to publish a report from the workshop in a refereed journal and to print an NICHD monograph with the salient presentations, conclusions and recommendations. In September, 1983, the Section convened a small group of experts to discuss new avenues of research in SIDS. Participating in thediscussion were several NICHD intraumural scientists.

Dr. Charlotte Catz is the NICHD representative to the DHHS Committee to Coordinate Environmental and Related Programs (DHHS-CCERP). She also is a liaison representative of the NICHD to the Committee on Drugs of the American Academy of Pediatrics, and serves as an ex-officio member of the Maternal and Child Health Research Grants Review Committee of the Health Resource Services and Administration.

Dr. Donald McNellis is the NICHD liaison representative to the Committee on Fetus and Newborn of the American Academy of Pediatrics. He is also a liaison to the Committee on Obstetrics: Maternal and Fetal Medicine of the American College of Obstetricians and Gynecologists. Dr. McNellis also serves as obstetric-gynecologic consultant to the Board for Correction of PHS Commissioned Corps Personnel Records.

Dr. Joseph Hwang was invited by the Fogarty Institute to participate as a scientific translator at meetings with members of the Health Ministry of the People's Republic of China.

Table 2b.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1983
PREGNANCY AND PERINATOLOGY SECTION

Funds (in thousands)

Health Area	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	234	$28,666	202	$25,765	174	$17,226	13	$7,913	15	$626	20	$1,038	12	$1,863
High-Risk Pregnancy	74	9,983	62	8,462	54	4,906	5	3,426	3	129	5	242	7	1,279
Fetal Pathophysiology	56	7,431	52	7,176	42	4,587	4	2,340	6	249	3	181	1	74
Premature Labor and Birth	38	4,449	38	4,449	35	3,378	2	1,032	1	39	-	-	-	-
Disorders of the Newborn	50	4,981	36	4,237	31	3,000	2	1,115	3	121	12	615	2	129
Sudden Infant Death Syndrome	16	1,823	14	1,442	12	1,355	-	-	2	87	-	-	2	381

Notes: 1) Excludes scientific evaluation grants.
2) The Minority Biomedical Support grants (S06) are included with the research projects.

NICHD-OPE-PAS
July 8, 1983

Nutrition and Endocrinology Section

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PROGRAM ACTIVITIES

Emphasis Areas

The Nutrition and Endocrinology Section supports research and training on developmental aspects of nutrition, endocrinology, physiology, and physical growth. These have been organized under the following areas:

1) Maternal-fetal nutrition
2) Infant nutrition and breast-feeding
3) Cultural, behavioral, and developmental aspects of food and nutrition
4) Developmental gastroenterology
5) Obesity and nutritional antecedents of adult disease
6) Growth factors and developmental endocrinology
7) Developmental Physiology

Contract Program

Since 1978 NICHD has been especially concerned with the composition, health values, and developmental importance of human breast milk for the normal newborn as well as the high risk infant. To meet the special needs of this field a coordinated research contract program was established to expand the base of knowledge on the detailed composition and function of the many constituents of human milk. This unique biological fluid is, as a result of these efforts, now recognized as a valuable source of nutrients, growth factors and antimicrobial activity that has great value for newborn infants and, particularly, infants born with low-birth-weights. The status of each contract is appended to this report. In FY 83, support of these contracts amounted to $2,520,000.

Research Training Program in Nutrition and Endocrinology

In FY 83 the Section funded four Institutional National Research Service Awards (NRSAs). One of the Institutional NRSAs is devoted to developmental aspects of nutrition. These six post-doctoral fellows are pursuing nutritional needs of prematurely-born babies and babies born at term, especially amino acid and essential fatty acid requirements. The other three Institutional NRSAs are concerned with developmental aspects of endocrinology and physiology. The eleven post-doctoral fellows supported by these awards are working on projects that vary from studies of mechanisms of gonadotropin release to opiate receptor function. In the area of developmental nutrition the Section currently funds one Individual NRSA. The Section also funds five Individual NRSAs in developmental endocrinology.

Financial Support

As of June, 1983, the Section supported 188 projects at a level of $18,279,000. These projects are analyzed according to programmatic mechanism in Table 2c. Two-thirds of the total budget supported nutrition-related research, one-quarter supported endocrine-related research, and the remainder supported research on developmental physiology and physical growth.

In FY 83 the Section received 189 research grant and research training grant applications. Of these 145 were approved and 37 were funded by July 1, 1983.

RESEARCH HIGHLIGHTS IN NUTRITION

Maternal-Fetal Nutrition

One of the most important of the Section's programs, especially from a preventive point of view, is that of maternal-fetal nutrition. This research explores the complex nutritional relationship that exists between the mother and her fetus.

Maternal-fetal iron transfer across the placenta is vital for fetal growth. During pregnancy the fetus accumulates large amounts of iron in order to support erythropoiesis, and maternal iron must be actively transported against a trans-placental concentration gradient. Investigators working with a guinea pig model have now shown that ferric placental iron moves from maternal to fetal circulations by passing through endothelial cell junctions, perhaps in conjunction with a low molecular weight carrier protein.

NICHD-supported investigators working on placental transport of calcium have recently isolated and purified human placental calcium-binding protein. Cellular localization studies have revealed that the calcium binding protein increases in concentration during gestation and is primarily associated with the maternal face of the chorioallantoic placenta and the uterine wall.

A major unsolved problem in the area of maternal-fetal nutrition is that of intrauterine growth retardation (IUGR). The etiology of IUGR appears to be multifactorial in nature. One NICHD-supported investigator is studying the role of polyamines in maternal circulation. Polyamines may be physiological indicators that would allow one to differentiate between normal and abnormal pregnancies. Polyamine levels increase in amniotic fluid during gestation and presumably reflect fetal growth. Therefore, they may provide a reliable marker for intrauterine growth retardation.

Other NICHD-supported investigators have produced sheep models of IUGR in order to assess the feasibility of intrauterine nutritional therapy delivered directly to the fetal stomach. Results show that infusion of a solution of glucose and amino acids during the period of maternal dietary restriction significantly increases birth weight and crown-rump length when compared to unsupplemented fetuses of nutritionally deprived ewes. This discovery may pave the way for the testing of intrauterine nutritional therapy in humans. In July, 1983, a research workshop was held on IUGR that emphasized promising new diagnostic and therapeutic approaches to the problem.

Infant Nutrition

The Section's largest program is that of infant nutrition. Research interests include the nutrient requirements of normal, premature, and growth-retarded infants, as well as analysis of human milk, cow's milk, and synthetic formulas in relation to optimal infant development.

The biochemical immaturity of premature infants presents challenging problems that must be solved in order to design appropriate feedings for their enteral and parenteral nutrition. These new feeding regimens are rooted in many basic research findings. For example, much has recently been learned about the complicated composition of human milk and how it reflects the metabolic needs of the newborn. Milk is not just a fluid containing nutrients. It is composed of a large array of constituents, many of which have important non-nutritive functions. Human milk contains numerous enzymes, one type of which (lipases) digest lipids. There appears to be a concerted action by the babies' oral and intestinal lipases in conjunction with the milk-derived lipases to digest the lipids contained in milk.

The structure of the milk fat globule examplifies the complicated packaging of milk components. The globule is surrounded by a membrane that is derived from the breast milk cell. Ultramicroscopic observation shows this membrane to have whisker-like filaments on its outer surface. Human milk is the only species examined so far that has these structures. This observation may be the first clue as to how specific lipases are able to recognize milk lipids for the purpose of digestion.

In view of the importance of breast milk to the growing infant, the Section supports research aimed at identifying the biological and psychosocial factors that motivate mothers to breast-feed their infants. A related research question also being studied is what factors contribute to unsuccessful breast-feeding and early weaning. As a result of renewed interest in the use of human milk in feeding of the low-birth-weight infant an important clinical question arises. What support mechanisms are necessary to encourage the mother of a low-birth-weight infant to lactate and contribute her milk to the nutritional support of her hospitalized infant? Several studies are investigating the composition of breast milk of mothers who deliver premature infants. As part of these efforts data are also being gathered on the factors that contribute to the mother's interest in breast-feeding. Thus, these at-risk infants will receive the beneficial properties of human milk (such as immunologic factors) and will not be automatically excluded from the opportunity to breast-feed simply because they were born too early.

The expanding awareness of the nutritional value of breastmilk has stimulated the establishment of an increasing number of milk banks. These milk banks serve a wide variety of purposes which include supplying milk for clinical care and clinical investigations on infant nutrition; the banking of milk for later feeding to normal infants; and the occasional storage of milk by a mother for feeding to her infant at a time when she is unavailable to breast-feed. A soon-to-be published summary of an FY 82 workshop on breast milk banking presents practical and ethical guidelines for milk banks and identifies research opportunities in clinical use of human milk.

Cultural, Behavioral, and Developmental Aspects of Food and Nutrition

The Section supports research that emphasizes the roles played by various nutrients in cerebral and somatic development. These studies are designed to ascertain the effects of general and specific kinds of undernutrition on physical growth and cognitive development during infancy and childhood. Iron deficiency as well as iron-deficiency anemia have been linked to various

cognitive deficiencies during development. The Section supports research projects that focus on understanding this and other relationships of nutrition with cerebral development.

Childhood and adolescence represent times when the individual is increasingly in control of the types and quantity of food to be consumed. Understanding the factors that influence selection of food and amounts consumed is, therefore, an important area of research. The NICHD has supported some of the seminal research on the factors that influence food choices in young children. These studies have shown, for example, the enormous power of televised commercial messages in shaping children's food selections.

The development of the child's conception of food follows a sequence. Children under three years seem willing to accept anything as food and will reject items only if they are distasteful. Gradually, rejection because of anticipated harm appears. Rejections as inappropriate or disgusting appear last. Rejection of foods because of contact with offensive substances, a hallmark of disgust, does not appear until at least age 6. These investigators report the first substantial within-culture correlation between food attitudes of parents and their children. This occurs not in the area of food preference, but rather in the area of disgust and contamination sensitivity.

NICHD-supported investigators have shown that the rates of child malnutrition (up to 96%) in Papua-New Guinea follow cultural boundaries rather than environmental ones. The highest reported rates of child malnutrition are found where traditional proscriptions against feeding young children animal protein are followed on the grounds that such foods will cause children to sicken and die. The cultural basis for these proscriptions is under study.

Studies have also begun on the social etiology of anorexia nervosa, including societal, family, and personality factors in adolescents who develop this disorder. Rather than a true loss of appetite, anorexics have a phobia of ingesting food and gaining weight. Many maintain an obsession with food and do not report a loss of appetite. The role of standards of physical attractiveness and ideal body physique also are being investigated by comparing anorexics and normal-weight control subjects. The results obtained suggest that even normal-weight adolescent American females exhibit a significant preoccupation with food and dieting and a pervasive dissatisfaction with their bodies. The control group females indicated a desire to be thinner than their present body weight.

Developmental Gastroenterology

The goal of the Section's program in developmental gastroenterology is to understand events governing development of the gastrointestinal tract from fetal life to adulthood. Emphasis is placed on the role of nutrients as effectors of gastrointestinal development. Research is underway on how components of human milk and colostrum serve to stimulate gastrointestinal development as well as to protect the gastrointestinal tract from disease.

Neonatal events impose unique adaptive need on the gastrointestinal tract. The newborn infant possesses only a limited supply of energy reserves which

are stored as body fat, and the infant has only a moderately developed intestinal tract. At birth, nature orchestrates the release of a complex series of secretions from the oral cavity, stomach, and intestine, each of which plays a critical role in digestion and absorption. Several studies are underway on the progression of the digestive processes that appear near the time of birth. It is clear that absorption of fats from the diet are critical to the newborn infant's energy needs. Therefore, an animal model system has been developed that allows for analysis of bile acid secretion in the newborn, and another study is focused on the role of fat-digesting enzymes secreted in the mouth and in the stomach.

Obesity and Nutritional Antecedents of Adult Disease

A crucial research issue that is being addressed by the Section concerns the antecedents of obesity. The ultimate goal is to identify determinants of obesity in childhood and adolescence in order to identify those individuals at high risk of becoming obese later in life and to design various kinds of preventive therapy. Of great interest is that infantile obesity does not predict adult obesity. However, obesity in childhood after age four does predict obesity in adulthood. NICHD-supported investigators have analyzed data on obesity generated by the Ten-State Nutrition Survey (N=30,000) and the Tecumseh Study (N=4,000). They have found that obesity is not randomly distributed through the population. Rather, obesity falls along socioeconomic gradients and is most common in lower-income females and in median income males. In the affluent of both sexes obesity is least often encountered. These statements apply to both Blacks and Whites in the United States. Although the Black female is generally fatter than the White female, at comparable levels of education, income, or occupation, Blacks and Whites are comparably fat or lean. Obesity also follows family line. This is best dramatized by comparing the progeny of two obese parents or two lean parents. With two obese parents the child has a 300% greater chance of becoming obese, and the child of two obese parents is, at adulthood, over 300% fatter than comparable children of two lean parents.

The Section continues to support a longitudinal study of the development of obesity in 170 children followed from birth. Analysis of obese and non-obese 12-year-old children revealed that there were no significant differences related to breast or bottle feeding in infancy and that obesity at 12 years of age is not related to type of infant feeding.

Johnston et al have completed a longitudinal study of fat cell growth in infants. They found that infants who were fed at infrequent intervals had greater weight for height ratios than those who were fed on demand. They also reported an inverse relationship between age at introduction of solid foods and infant weight for height ratio. NICHD-supported investigators have developed behavioral paradigms to control body weight in high-risk children. The study involves long-term follow-up of a group of preadolescent obese children who participated in a trial to determine the effects of targeting parent and child or child alone in a behavioral weight control program. After three years of follow-up, these investigators showed differential treatment effects for maintenance of non-obesity: eighty-three percent of the children who achieved non-obesity at eight months were still non-obese if their parents participated, while only 30 percent of children in the child-alone group remained non-obese.

RESEARCH HIGHLIGHTS IN DEVELOPMENTAL ENDOCRINOLOGY

The field of developmental endocrinology encompasses studies of hormonal influence on growth and development, studies of growth factors, and studies of the development of the hypothalamic-pituitary axis in relation to the thyroid, adrenal glands, and gonads.

Treatment of Precocious Puberty with LHRH Analogue

Recently a promising treatment has been developed for the perplexing condition known as idiopathic central precocious puberty in which young children, or even toddlers, acquire mature sexual organs and secondary sexual traits. Until now treatment of this psychologically and socially disrupting disorder has relied on the administration of medroxyprogesterone or antiandrogens, neither with satisfactory results. Within the past two years many cases of precocious puberty have been successfully treated with a synthetic analogue of luteinizing hormone releasing hormone (LHRH). The synthetic decapeptide, a superagonist of LHRH, is modified at positions 6 and 10 and has an increased affinity for pituitary LHRH receptors and a longer half-life than LHRH. Initial results are most encouraging in that patients' gonadotropin levels revert to undetectable levels, and their sexual characteristics regress to pre-pubertal status. No deleterious side effects have been observed.

Short Stature and Human Growth Hormone

The imminent availability of large quantities of biosynthetic human growth hormone (hGH) represents a great accomplishment in the annals of modern endocrinology. From 1958 until 1982 the only treatment available for growth-hormone-deficient children was hGH extracted from pituitaries removed from human cadavers. This limited supply was sufficient to maintain growth in only about 1200 hGH deficient children per year in this country. Recently several exciting discoveries have been made in the therapy of short children which coincide with the advent of biosynthetic hGH.

Plotnick et. al. have identified a group of short children who are not demonstrably deficient in hGH but who have low levels of somatomedin C and who respond to the administration of exogenous hGH with accelerated linear growth. These investigators noted that biologically inactive growth hormone could account for their observations. Kowarski has since used a panel of 18 monoclonal antibodies directed against hGH to demonstrate the presence of aberrant hGH in short children with this syndrome. Recently Van Vliet et al have shown that short children with apparently normal hGH and normal somatomedin C will respond to the administration of exogenous hGH with accelerated linear growth. These discoveries about the ability of exogenous hGH to promote linear growth in the absence of demonstrable hGH deficiency, coupled with the availability of large amounts of biosynthetic hGH, will prove beneficial in the clinical management of short children in the near future.

Congenital Adrenal Hyperplasia

New and colleagues have reported novel clinical, genetic, and biochemical aspects of 21-hydroxylase deficient congenital adrenal hyperplasia (CAH). Their discovery of linkage between the genes of the HLA locus and 21-hydroxylase has made it possible in affected families to predict which

siblings are carriers and which siblings are genetically unaffected. By examining cases of genetic recombination between the HLA-B locus and the gene for 21-hydroxylase, it has been established that the allele Bw47 is the one most commonly associated with classical 21-hydroxylase deficiency. This allele carries a relative risk of 15.4. Late onset and cryptic forms of the disorder are associated with genetic markers HLA-B14, HLA-DRI, and Properdin factor BfS. Individuals with the cryptic form of CAH appear to be double heterozygotes and carry one allele for classical CAH and one for cryptic CAH.

Genetics of Susceptibility to Insulin-Dependent Diabetes Mellitus (IDDM)

Genetic studies of families containing at least one insulin-dependent diabetic have shown that non-diabetic siblings who have an HLA type identical to that of their diabetic sibling run a risk of becoming diabetic 50 times greater than that of children from non-diabetic families. Barbosa et al studied more than one hundred families containing two or more insulin-dependent diabetics. They confirmed that there is a diabetes-susceptibility locus in the HLA region of Chromosome 6. Moreover, they showed that the diabetes-susceptibility gene exists in extremely tight linkage with HLA types D_3 and D_4. Children who have both D_3 and D_4 antigens run a high risk of becoming diabetic even if no other family member is diabetic. On the other hand, children who carry HLA types B7, Dw2, or DR2 have relative risks for IDDM below 1.0. Genetic research such as this represents a step toward the ultimate prevention of insulin-dependent diabetes mellitus by providing a means to identify those individuals who are most susceptible to Type I diabetes and by guiding genetic researchers to isolating the actual gene products of these protective loci.

RESEARCH HIGHLIGHTS IN DEVELOPMENTAL PHYSIOLOGY

This program is concerned with the development of physiologic feedback pathways by which homeostasis is achieved in blood volume, blood pressure, and electrolyte balance. Recently, Hamlyn et al reported an important clue to explain the etiology of essential hypertension, i.e., permanently raised arterial blood pressure not secondary to any known cause. They demonstrated the presence of an inhibitor of (Na+ - K+) ATPase in the plasma of subjects with essential hypertension. Their data support the view that this inhibitor is a natriuretic hormone secreted by hypertensive subjects in increased quantities as a compensatory mechanism to enhance sodium excretion. It may produce hypertension as a side effect by increasing Na+ levels in vascular muscle cells, leading to net accumulations of intracellular Ca++ and hence increasing contractility.

STAFF ACTIVITIES

The professional staff of the Section represents the NICHD on a number of groups and committees in both the public and private sectors. Dr. Gilman Grave, the Section Chief, serves as the NICHD Representative to the NIH Nutrition Coordinating Committee. Dr. Grave also represents the Institute on the NIH Diabetes Mellitus Coordinating Committee as well as the Diabetes Mellitus Interagency Coordinating Committee. He serves as an alternate ex-officio member of the National Diabetes Advisory Board. In FY 83 a new trans-NIH ad hoc Workgroup on Inherited Metabolic Disorders was formed. Dr. Grave represents the NICHD on this workgroup. He worked with other

Institutes' representatives to plan a U.S.-Japan re[illegible]nference on this topic which was held in March, 1983.

Dr. Thorsten Fjellstedt represents the NICHD on the [illegible]estive Diseases Coordinating Committee and also is liaison to the U.[illegible]-Japan Cooperative Biomedical Sciences Panel on Malnutrition. He serves as an alternate ex-officio member of the National Digestive Diseases Advisory Board. Dr. Fjellstedt serves as NICHD liaison representative to the Committee on Nutrition of the Mother and Preschool Child of the Food and Nutrition Board of the National Academy of Sciences. He also serves as liaison representative to the Committee on Nutrition of the American Academy of Pediatrics. Dr. Fjellstedt acts as the NICHD designated representative to the Board of Scientific Counselors of the USDA-Children's Nutrition Research Center in Houston, Texas.

Table 2c.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1983
NUTRITION AND ENDOCRINOLOGY SECTION

Funds (in thousands)

Health Area	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	175	$18,279	149	$15,301	135	$13,463	3	$1,446	11	$392	11	$458	15	$2,520
Developmental Gastroenterology	20	1,676	20	1,676	20	1,676	-	-	-	-	-	-	-	-
Childhood & Developmental Nutrition	16	1,504	14	1,339	14	1,339	-	-	-	-	2	165	-	-
Infant Nutrition	37	5,293	25	3,339	21	1,862	3	1,446	1	31	-	-	12	1,953
Obesity & Antecedents of Adult Disease	12	1,462	12	1,462	10	1,384	-	-	2	78	-	-	-	-
Behavioral & Cultural Aspects of Nutrition	12	1,325	10	861	9	822	-	-	1	39	-	-	2	464
Maternal-Fetal Nutrition	9	961	9	961	9	961	-	-	-	-	-	-	-	-
Adolescent Nutrition	3	126	3	126	2	96	-	-	1	30	-	-	-	-
Nutritional Status	2	103	2	103	1	61	-	-	1	42	-	-	-	-
Developmental Endocrinology	51	4,507	42	4,131	39	4,017	-	-	3	114	8	274	1	103
Developmental Physiology	9	614	8	596	6	537	-	-	2	59	1	18	-	-
Physical Growth	4	709	4	709	4	709	-	-	-	-	-	-	-	-

Note: 1) Excludes scientific evaluation grants.

NICHD-OPE-PAS
September 12, 1983
Revised

Mental Retardation and Developmental Disabilities Branch (MRDD)

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OVERVIEW

The NICHD, within the NIH, has primary responsibility for research and research training concerned with mental retardation. This interest is expressed categorically through the Institute's Mental Retardation and Developmental Disabilities Branch (MRDD) of its Center for Research for Mothers and Children (CRMC). The MRDD Branch supports research into the biological, behavioral and social processes which contribute to, or influence the development of, retarding disorders. The Institute employs research grant mechanisms, supports special research facilities as the Mental Retardation Research Centers (MRRC's), disseminates scientific and public information, and provides contract support for research to accomplish its goals. The Institute's research programs and resources provide research knowledge and understanding applicable not only to mental retardation but to other closely related developmental disabilities as well.

The primary objective of mental retardation research is to develop and support research aimed at the prevention of mental retardation and, when this is not possible, to effect its amelioration. All biomedical, behavioral, and social disciplines capable of contributing to the understanding of the etiology, epidemiology, pathophysiology, diagnosis and/or evaluation, prevention, and amelioration of mental retardation contribute to the mental retardation research effort.

PROGRAM ACTIVITIES

FINANCIAL SUPPORT

As of June, 1983, the Mental Retardation and Developmental Disabilities Branch (MRDD) supported 403 grant projects and contracts in the amount of $28,013,000. Table 3 shows the allocation of projects and funds in the major areas of mental retardation research activity which include etiology/pathophysiology; epidemiology; diagnosis and/or evaluation; prevention; and amelioration. As in past years, basic studies concerned with the etiology and pathophysiology of mental retardation syndromes were supported at a level of $15,446,000 and constitute the major concentration of Branch effort. The second largest concentration of Branch support is in the area of diagnosis and/or evaluation. Here, 120 projects were supported in the amount of $8.2 million.

The MRDD Branch places primary reliance upon the research grant mechanism to accomplish its research objectives. For this reason, only one contract in the amount of $52,000 was supported in FY 1983. Details of this contract are provided at the close of this report.

RESEARCH TRAINING

Twelve institutional training grant awards and 2 fellowship awards totaling $1.463 million were supported by the Branch in FY 1983 (Table 3). This represents a decline from FY 1982 when the Branch supported a total of sixteen training grant awards. Branch support of research training is evenly distributed between the biomedical and the behavioral and social sciences, and some training grants give emphasis to interdisciplinary training. Branch programming efforts are currently directed toward expanding support of interdisciplinary training.

MENTAL RETARDATION RESEARCH CENTERS (MRRC)

The Branch has administrative responsibility for the Mental Retardation Research Centers--12 in number--constructed under the authority of P.L. 88-164. The MRRC's were constructed to conduct research and research training in mental retardation and related aspects of human development. Under the provisions of the Act, the centers contracted to use the facilities for their intended purpose for a minimum of 20 years. On average, the centers have now completed about 14 years of this obligation.

The MRRC's form our nation's major research resource for the investigation of the problem of mental retardation in all its aspects. In keeping with the multiple and diverse causes and the complex nature of the problem, the centers bring to this research and research training enterprise a strong capability for multidisciplinary and collaborative research between the biomedical, behavioral and social sciences in laboratory and field settings. Through these efforts, the centers have contributed increasingly to an understanding of the etiology and pathogenesis of mental retardation and related central nervous system disorders and to programs of prevention, treatment and amelioration. Although a significant portion of the research portfolios in the centers consists of basic studies fundamental to an understanding of biological and behavioral processes in animal and human organisms, considerable attention is directed toward seeking solutions to practical issues and problems. Thus, investigators in the centers are exploring the impact on retarded development of deinstitutionalization, normalization, mainstreaming, and various forms of community placement. These efforts are expected to provide an empirical base for large-scale intervention and amelioration programs in the years ahead.

Research in these areas is made possible by the vigorous outreach activities of center scientists, administrators, and communication specialists to community education, health and social service systems. In addition, most of the centers have very close working relationships with public or private residential facilities for the mentally retarded which permit access to subject populations and the development and evaluation of enriched environmental settings. As a consequence of these studies and others in community-based preschool and day care programs, models for effective intervention are being developed and applied in many communities and school systems throughout the country.

The range of research studies being conducted in the MRRC's encompasses every known major dimension of the problem. This concentration of activity is supplemented by the work of investigators located in other universities, agencies, and research settings. The activities described in the section which

Table 3.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1983
MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES BRANCH

Funds (in thousands)

Program Category	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	149	$28,013	133	$26,416	93	$9,661	31	$16,336	9	$419	14	$1,463	2	$134
Etiology/Pathophysiology	82	17,319	74	16,437	48	4,760	21	11,435	5	242	7	831	1	52
Epidemiology	2	483	2	483	2	483	-	-	-	-	-	-	-	-
Diagnosis and/or Evaluation	49	7,616	41	6,900	32	3,153	7	3,672	2	76	7	633	1	82
Prevention	5	1,302	5	1,302	3	454	2	848	-	-	-	-	-	-
Amelioration-Education	6	780	6	780	5	399	1	381	-	-	-	-	-	-
Amelioration-Medical Treatment	5	513	5	513	3	412	-	-	2	101	-	-	-	-
Other (includes implementation grants)	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Note: Excludes scientific evaluation grants.

NICHD-OPE-PAS
September 13, 1983
Revised

follows represent a few of the research accomplishments and highlights from the Branch portfolio during this fiscal year.

RESEARCH HIGHLIGHTS

The broad scope of research activities supported by the Branch precludes complete reporting. The selected research highlights which follow, organized under the rubrics of biomedical and behavioral and social sciences research, are provided to indicate the broad nature of the Branch effort.

BIOMEDICAL RESEARCH

Down Syndrome

The incidence of Down syndrome (D.S.) has been decreasing for the past several years. In 1960, the incidence was 1.33 cases per 1,000 births, while in 1980 the incidence was 0.73 per 1,000 births, a drop in frequency of 45%. Although prenatal diagnosis of high-risk pregnancies and elective abortion contributed some to the drop in incidence, demographic shifts in the U.S. population have contributed more to this decline.

It is a well known and universally accepted fact that the incidence of D.S. increases with advancing maternal age, particularly at age 35 and over. The number of babies born by women in this age group dropped from 10.8% in 1955 and 1960 to 4.6% in 1980, a decrease of about 51%. But this trend will probably change in the foreseeable future. The number of women 35 years of age or older is increasing. Census Bureau projections show that the female population in the 35-44 year group peaked in 1960 to 34%. The number of women in this age group has been going up since 1970, when the proportion dropped to an all-time low of 24.7%. In 1983, 27% of women are between 35-44 years and it is projected to increase to 33% in 1990. It can be anticipated that the incidence of D.S. will go up, with a concomitant increase in the request for mid-trimesteamniocentesis or first trimester diagnosis using placental biopsy.

For the past five years, NICHD has been supporting a project which deals with the development and distribution of an animal model for genetic disorders with particular emphasis on trisomy 21 (Down syndrome). The use of mouse models for cytogenetic defects is based on the assumption that, although the exact clinical manifestation may not be the same, the mechanisms for the production ofabnormalities probably are similar. The development of such an animal model wowould allow many studies which will be difficult to carry out in man.

The mouse model for D.S. is smaller than its normal littermates, has a high frequency of congenital heart defects, small and less cellular placenta, a smaller brain which is also less cellular, and flattened base of the skull. Distribution of the animal model will continue to facilitate anatomical, embryological, and biochemical studies. Behavioral studies on the mouse model are planned in the future.

Phenylketonuria (PKU)

Phenylketonuria is a genetic disorder in which the affected persons are unable to metabolize phenylalanine, an amino acid which is essential for normal growth and development. It is associated with severe mental retardation, behavioral problems, epilepsy and other signs of neurological impairment. The Institute is supporting a collaborative study to determine the effect of diet discontinuation on the development of PKU children who had been on a phenylalanine restricted diet since infancy. At age six years, with parental consent, each child was randomly assigned to either continue on the diet, or to discontinueand be free to eat a normal diet. At the age of 8 years, the IQs of childrenwho stayed on the diet are comparable to the IQs of their non-PKU siblings, while the IQs of those who discontinued the special diet were significantly lower than their normal siblings, as shown in the following table:

Eight Year WISC	Continued on Diet		Discontinued on Diet	
	Mean I.Q.	p value	Mean I.Q.	p value
6 Verbal Scale				
PKU's @ 8 years	103.1		98.0	
Sibs @ 8 years	102.3	.803	108.1	.001
Performance Scale				
PKU's @ 8 years	103.8		98.5	
Sibs @ 8 years	103.8	.990	111.1	.001
Full Scale				
PKU's @ 8 years	103.7		98.1	
Sibs @ 8 years	103.3	.882	110.5	.001

The investigators concluded that despite early and optimal treatment, high phenylalanine levels after age 6 years do represent a risk factor to which many of the PKU children who discontinued their special diet are vulnerable. The investigators recommend that children with PKU be maintained on a phenylalanine-restricted diet through adolescence. Since some children who discontinued the diet have maintained or achieved even higher IQs (compared to their IQs before the diet was discontinued), individual differences need to be considered in deciding whether or not to discontinue the diet.

An emerging problem that NICHD is currently addressing is the effect of high levels of phenylalanine during pregnancy on the developing fetus. Since PKU

women who are maintained on a normal diet during pregnancy are known to be at a high risk to give birth to physically defective and mentally retarded babies, the Institute will soon initiate, through the contract mechanism, a clinical trial on the effects of phenylalanine restriction administered prior to and during conception on pregnancy outcome.

Another investigator, who is partially supported by NICHD, proposes to isolate and characterize the human phenylalanine hydroxylase gene (the missing enzyme in PKU) using recombinant DNA technology. This investigator has already isolated the complementary DNA from rats and a human subject. He will compare the structural organization and nucleotide sequence between the cloned normal and defective gene. The investigator will utilize the information obtained from these studies to develop a simple and reliable genetic mapping method for carrier detection and prenatal diagnosis of PKU. The phenylalanine hydroxylase gene has been tentatively "mapped" on chromosome number 12.

Neural Tube Defects (NTD)

Neural Tube Defects (anencephaly, encephalocele, spina bifida) constitute one of the most common congenital abnormalities and are generally accepted to be caused by genetic and environmental causes. Preliminary results from the United Kingdom, where the incidence of NTD is higher compared to the U.S., suggest that multivitamin supplementation during pregnancy of women with a history of previous NTD births significantly reduced the recurrence rate of NTD when compared with unsupplemented mothers. Because of the non-random assignment of subjects and controls, the results of the study are open to question, especially since the supplemented group included a disproportionate number of women from high socioeconomic status. To correct the deficiencies in research design, the medical Research Council will initiate a randomized clinical trial in the United Kingdom.

NICHD is currently supporting a project dealing with the prevention of NTD by folate supplementation prior to and during pregnancy in the golden hamster. This animal model has a 17% spontaneous rate of occurrence of NTD. Preliminary results based on a limited number of animals suggest that, within a given dose range, folate supplementation can reduce the incidence of NTD in this animal model.

The Institute recently convened a group of consultants with expertise in the various aspects of NTD. The purpose of the workshop was to discuss the status of the science in this field and to provide guidance to Institute staff on potentially fruitful research approaches. It was the consensus of the group that NICHD should address basic research problems relevant to NTD, including the use of animal models, neuroembryology, and biochemistry, particularly involving folates, other vitamins, and trace metals. The group felt that, instead of embarking on a clinical trial, NICHD should assess the outcome of the controlled clinical trial soon to be started in the United Kingdom.

Krabbe's Disease (Globoid Cell Leukodystrophy)

Krabbe's disease is a hereditary neurologic disorder characterized by irritability or hypersensitivity to external stimuli beginning in early infancy and rapidly progressing to rigidity of the body, hyperactive reflexes, swallowing difficulties, and failure of normal motor and intellectual

development. The condition is caused by the absence of the enzyme, galactocerebroside beta-galactosidase. Patients rarely survive beyond the second year. There is no specific treatment for affected patients but prenatal diagnosis is available by demonstrating the absence of the enzyme on cells obtained from amniotic fluid.

In 1980 a group of investigators from the Jackson Laboratory in Bar Harbor, Maine described a mutant mouse which they called the "twitcher." In the initial report, the presence of globoid cells in the mouse suggested that this was an anatomically true model of Krabbe's disease. A group of scientists from the Mental Retardation Research Center at Albert Einstein College of Medicine subsequently demonstrated a genetic deficiency of the enzyme in the "twitcher" mouse. The same investigators clearly showed that the affected animal, the carriers, and normal mice can be distinguished biochemically, even before clinical signs become evident, by the amount of enzyme obtained from clipped tails. These findings were further confirmed by measuring enzyme levels in brain and liver tissues. These scientists also succeeded in maintaining tissue cultures of spinal cord obtained from the mutant embryos. The spinal cord developed and started myelinating normally. Then, evidence of myelin degeneration appeared around 35 days. Although the myelin degenerated progressively, the spinal cord in culture survived for three months, much longer than the life span of the affected mice. Since the tissue culture environment can be manipulated experimentally, the system is expected to provide a useful tool for future trials of enzyme supplementation.

Prematurity in Primates: Causes, Effects, Prevention

A group of behavioral and biomedical scientists at the Child Development and Mental Retardation Center at the University of Washington is engaged in a collaborative project to identify factors which contribute to offspring mortality, prematurity, and delayed or retarded growth and behavioral development. Their observations indicate that certain groups of monkeys have either a high or a low risk of reproductive failure. In order to study this phenomenon further, they use a rat embryo culture technique developed by a collaborator at the University of Connecticut. Rat embryos were isolated after nine days and cultured for 48 hours on serum samples from female monkeys with histories of infrequent or frequent fetal wastage. All serum samples were obtained from monkeys bred at the Primate Field Station at Medical Lake, Washington. The samples were coded and the reproductive histories of the donors were not disclosed until the embryo culture test was completed and evaluation of the embryos was made. The serum classifications coincided with the reproductive histories of the donors for 8 of the 12 low-risk breeders and 12 of the 14 high-risk breeders. This project provides an opportunity to search for a possible relation between reproductive history and serum teratogenicity. The investigators conclude that these results would be expected if such factors as endocrine dysfunction, immunological incompatibility, nutritional deficiencies, and chronic infectious agents--which are implicated in human fetal wastage--cause comparable problems in monkeys.

BEHAVIORAL AND SOCIAL SCIENCES RESEARCH

Early Identification of Risk Infants

The first step in treating retarded individuals is identification of those who are at risk to develop handicapping conditions. Behavioral researchers have been

developing methods to assess individuals suspected of having a variety of handicaps. It has long been thought that early identification may lead to early treatment which may avoid the development of serious handicaps. In one laboratory at the MRRC at Albert Einstein College of Medicine, scientists have been studying very low birthweight infants, a group thought to be at great risk for developmental disabilities. These investigators have been measuring brain responses to different classes of sound stimuli (auditory evoked potentials) in infants with normal birthweights compared with those of very low birthweight infants. They find that the low birthweight infants show less mature responses to the sounds until three months of age. This transient delay in maturation of the cortical areas concerned with the acoustic analysis of speech sounds might interfere with the development of auditory processing. This might account for the higher incidence of language-related cognitive deficits often observed during the school years in high risk infants. It is expected that this technique might be used to identify infants who are at risk for specific disabilities in auditory processing.

Another research team has been studying a group of low birthweight infants into the early childhood years. This group of infants came from both middle and low income families. It was found that, although there were no differences between the two SES groups prior to the second year, by age 3 1/2 marked differences in IQ were detected. The low SES children showed a high proportion of borderline and retarded levels of performance. In addition, 30% of the entire sample showed severe behavioral/emotional problems by age 3 and 4 and these problems seemed to be associated with low IQ. Since the effects of maladjustment and social class are believed to be additive, all maladjusted low SES children were significantly retarded at 3 1/2 years whereas equally disturbed middle class children showed normal IQ's. These findings suggest further that low income children who are also at risk biologically are at greatest risk for retardation and developmental disabilities and should be the target for early intervention efforts to ameliorate their delayed development.

At the University of North Carolina MRRC, researchers have developed an assessment instrument for handicapped infants and young children, the Carolina Record of Individual Behavior. More than 360 children under 6 years with various handicapping conditions were administered the scale. The scale has been found to be suitable for use with mentally retarded, orthopedically handicapped and auditorily handicapped children. Through the identification of strengths and deficits of the individual child, the scale may be useful for planning and evaluating intervention efforts. Other researchers supported by the MRRC Program have been developing techniques for the identification of specific neuromotor problems associated with speech motor control. This includes the development of a national facility for speech motor research using X-ray microbeam technology. This facility will make possible assessment of speech movements, muscle activity, aerodynamic and acoustic signals simultaneously without the dangers of high radiation exposure associated with earlier techniques. The research facility is expected to greatly enhance research efforts into the speech deficits associated with mental retardation and developmental disabilities.

Perceptual and Attentional Processes

Attentional processes are basic for the development of intelligent behavior. In one laboratory at a MRRC an investigator is studying how input from the senses is affected by attention. She uses measures of attention such as heart rate slowing and direction of gaze which can be studied in handicapped as well as normal infants. Recently, she found that when attention is focused on one kind of stimulation, acoustic or visual, it affects the response to other probe stimuli. Eye blinks elicited by acoustic probes were larger during listening and smaller during looking. The reverse was true for blinks elicited by visual probes. The effects were exaggerated if the focusing stimulation was more interesting. Since eyeblinking is a brainstem reflex, the findings show that attention can filter input by low level modalities. This ability is present in the normal infant as early as the 16th week of life. Since many retarded children appear to have problems in focusing their attention, these findings may have relevance for understanding how attentional processes regulate information processing early in the lives of retarded children.

In some of the MRRC's investigators engage in research on basic processes prior to undertaking studies with handicapped populations. One such investigator has been studying infant perception of "biological motion". When a small number of lights are placed on the limbs and joints of a moving person, the motions of the lights (biological motion) are sufficient to enable adult observers to perceive immediately the activity of the moving person. This perception of biological motion has been suggested as an innate capacity of the visual system rather than one acquired through experience. As a test of this hypothesis, this research team conducted three experiments to study sensitivity to biological motion in infants. Three groups of infants were tested at 2, 4, and 6 months. Results of these experiments indicate that sensitivity to biological motion patterns becomes evident in infants between the ages of 4 and 6 months. These results suggest that the mechanism responsible for such sensitivity is largely intrinsic rather than acquired slowly through experience. Nevertheless, it is not obvious why the youngest infants did not exhibit this sensitivity. Perhaps a postnatal period of growth is required before such a mechanism becomes functional. These experiments may contribute to the growing knowledge base about innate and experientially based capacities. They certainly add to our understanding of the complexity of perception in young infants and might contribute to the development of techniques for identifying handicapped children at the earliest ages.

Learning and Cognition

For many years, investigators engaged in research on learning studied the optimal conditions for presenting material which is to be learned. Nevertheless, such experiments were never carried out using severely handicapped children. One group of investigators in MRRC recently compared the effects of three types of sequencing of learning of cognitive and motor skills: massed, distributed and spaced practice. Students living at home and those living in institutions were compared. Results indicated no differences for those living in institutions. Students living at home, however, showed superior performance for trials distributed over several days when compared to the other two types of sequencing. These results will contribute to the technology of instruction for severely handicapped learners.

One of the most important problems to be solved by researchers studying learning and cognitive processes is that of transfer from problems which are specifically taught to similar ones which are not taught. One team of researchers supported by the MRDD Branch has been studying this problem for a number of years. In the past they have investigated how the children go about solving problems presented to them by asking the children to verbalize the steps they went through to solve the problems. Using this information from earlier studies, the researchers designed tasks in which they provide help in the form of hints, clues or questions which will lead to correct solution of the problems. Most recently they have developed learning tasks in which they can systematically vary the complexity of the learning tasks and the degree of transferability of learned information to new tasks. They have approached this problem by studying children varying in chronological age as well as learning ability. Thus far, they have found that younger or lower ability children show difficulty when they mustmake flexible use of learned information. In one study of retarded children ranging in age from 8 to 11 years of age they found that more than half of the children were not able to learn to criterion. However, the children who did show learning did so with less help than younger non-retarded children. They were also able to show greater transfer than the non-retarded children. It is not yet clear why the retarded children showed this superiority of performance. The research team is presently following up their findings in order to further illuminate the process used by the retarded learners to solve the problems so efficiently.

At the Vanderbilt University MRRC, a team of researchers have been studying the learning process of slow learners in fifth grade. These investigators conducted two experiments in which they compared poor learners with successful learners using text material that varied in how much information was contained in the passage to be learned. They found that the poor learners given the explicit passages remembered as much about the material as the successful learners did. However, the poor learners did not show any transfer to less explicit passages. In a second experiment, the poor learners were given focused training and were found able to learn when tested with unexplicit material. This suggests that by modifying the material poor learners are expected to master their performance and their ability to learn can be greatly enhanced. The researchers refer to such enhanced material as "considerate texts". The findings also indicate that the training procedures they have developed, based on Feuerstein's "instrumental enrichment program" could be extended to many aspects of school curriculum to improve the learning ability and performance of poor learners.

At another MRRC, University of Kansas, researchers who have been studying how retarded adolescents learn have come to similar conclusions as the previously described findings. In this laboratory, the investigators found that if they modify the material to be learned to fit the capacity of the learners, some of the retarded children performed at the same level as a group of nonretarded learners using more complex material. These researchers discovered that among both retarded and nonretarded learners there were subgroups who showed comparable proficiency in learning. These investigators are presently following up their earlier findings to discover what distinguishes those children in each group who show high performance from those who show poor performance.

It is of interest to note that research supported by the MRDD Branch in cognitive processes has been progressing steadily. In the next few years, researchers studying cognitive processes among retarded children will be in a position to recommend specific strategies for teaching retarded children. The three laboratories which were referred to above are among those which have been moving toward making important breakthroughs in understanding how retarded children learn and hence how to best optimize their learning.

Amelioration and Treatment of Retarded Children

Among the research programs supported by the MRDD Branch, several are aimed at amelioration of handicapping conditions. These range from broad band interventions designed to prevent mental retardation in groups at risk for cultural-familial retardation to very specific treatments focused on particular developmental problems. Several of these will be described below.

An interdisciplinary team of researchers at the University of Washington MRRC's studied the effect of developmental therapy on motor-impaired children ranging in age from 3 to 15 years. Study participants were affected by mental retardation, autism and severe communication disorders but no known neuromuscular impairments. They were assigned at random to a once a week treatment, thrice a week treatment or no treatment. Results indicated that there were no differences between the two treatment regimens though both treatment groups showed gains in gross motor performance more than four times that of the control group. This study indicates that significant decreases in motor impairment can be obtained with only weekly therapy sessions. In times of limited professional resources, findings such as these are important in guiding how to allocate treatment regimens among those needing such services.

A research group at the Vanderbilt University MRRC completed a study testing the effects of semicircular canal stimulation on motor development and stereotyped behavior in developmentally delayed infants. The semicircular canals are sensitive to body motion and provide cues regarding position of the head and body. When the body experiences motion in any direction, receptors in the semicircular canals and other organs containing fluids are stimulated. It was hypothesized that providing stimulation of these receptors (vestibular stimulation) would foster the accelerated development of motor ability and the decline in stereotyped movement often seen in retarded children. In this study, the infants were rotated in a motor-driven chair at a velocity of 17 rpm for 10 minutes daily over a period of 2 weeks. Standard motor and reflex measures were taken before, during and after the rotation treatment period. Daily observations were made of the infants' stereotyped movements. Results of the study indicated that all of the infants in the study showed improved motor and/or reflex behavior as well as some amelioration of the stereotyped movements. These changes were attributed to the vestibular stimulation. Currently, these investigators are expanding their study to learn more about the effects of vestibular stimulation on infant behavior.

At the University of North Carolina MRRC researchers have been studying the effects of a preschool educational intervention program on low income children who are thought to be at risk for mental retardation. As part of this project, high-risk children who had been exposed to the intervention were compared with high-risk children who were not given the intervention and a low-risk

comparison group with regard to their beliefs in personal control over academic success. Among the high-risk control children no relationship was found between belief in personal control and academic success. In the other two groups the relationship was found to hold. These results support not only the importance of motivation to achievement but also the influence of socializing environments in establishing relations among beliefs in personal control, subsequent goal directed classroom behavior and achievement outcomes.

Personality and Adaptation

One of the important criteria used in judging whether a person is mentally retarded is adaptive behavior. Individuals who score low on tests of intelligence but show normal adaptation are usually not labelled as being retarded. Thus,it is important to have psychometrically adequate ways of measuring adaptive behavior. An investigator at one of the MRRC's has recently developed a new scale to measure personal competence in mentally retarded individuals. The Personal Competence Scale is a 20-item instrument designed to assess competence of mentally retarded adults. This broad bandwidth measure provides scores on three factorially derived scales as well as a total score. The three major dimensions of personal competence delineated were adaptive, cognitive and affective competence. These measures proved to be good predictors of both IQ and other measures of adaptive behavior. The advantage of the new instrument is that it can be administered quickly and provides a concise measure of personal competence. The developer of this instrument is continuing to study the usefulness of the scale for improving the adaptive behavior of retarded adults.

Community and residential rehabilitation programs experience considerable difficulty in providing effective treatment of mentally retarded adults with emotional and behavioral disorders. Of these disorders, conduct difficulties involving verbal and physical aggression, problems of temper and anger control, and related disruptive outbursts have been among the most resistant to change.

The effects of a self-management intervention program have been evaluated with groups of mentally retarded adults who present high-rate chronic problems of conduct in a vocational training setting. This program was developed and evaluated by researchers in one of the MRRC's. This intervention program teaches skills of self-instruction, self-monitoring, self-evaluation, and self-reward. The rationale for the program is to provide the mentally retarded adult with alternative behaviors which are incompatible with the conduct difficulties.

Results of the initial study demonstrated the effectiveness of the self-management program in eliminating high levels of verbal aggressiveness. The gains in treatment were maintained for at least 6 months after the end of the program. These findings suggest that mentally retarded persons with chronic high rates of behavior problems may be suitable candidates for cognitive behavior therapy intervention programs. The intervention program and evaluation study are presently being replicated at a training and evaluation center in Arizona.

Social Processes

It has long been recognized that retarded children, in addition to their limited intellectual capacities, may also have difficulties in interaction with other people. Several researchers supported by the MRDD Branch have been studying how handicapped children interact with one another and with non handicapped children. One group of researchers at a MRRC have been conducting a series of projects designed to understand how best to improve the social skills of handicapped children. One of the strategies they have explored is to train normally developing preschoolers to initiate interaction with handicapped peers. Following an experiment in which they were successful in increasing the interaction of the socially withdrawn handicapped children, the investigators conducted an experiment in which the intervention agent was also handicapped. Results of these experiments revealed that both normally developing and handicapped age-peers can be used effectively to increase the social behavior of handicapped children. As with adult-mediated interventions, no spontaneous maintenance and generalization effects were obtained with the peer social initiation technique and the lack of appropriate social stimuli in their educational settings probably was responsible for maintaining withdrawn social behavior. The investigators conclude that three factors may serve to limit maintenance and generalization: the predominance of socially unresponsive children in the classroom, a well-established friendship network and a history of negative social contact between target children and class peers.

Family Processes and Interaction

The influence of family factors on the development of intelligence in children at risk for mental retardation has been of interest to researchers for many years. Scientists at the MRRC at the University of North Carolina studied children at risk for sociocultural mental retardation from birth to four years of age. Maternal IQ was assessed prior to the child's birth and children's IQ and home environments were assessed at regular intervals during the first four years of life. By examining the influence of each of these factors separately, it was possible to determine their relative contribution to predicting the child's IQ at age four. Results indicated that as the child got older, the influence of the home environment including such factors as stimulating toys, number of books and maternal interaction, grew relative to that of the mother's IQ. This suggests that the quality of the home environment during the first four years of life is important in predicting the child's intelligence in families in which the child is at risk for sociocultural mental retardation. These findings mean that it may be possible to modify the home environment in such a way as to prevent or ameliorate sociocultural mental retardation.

At the MRRC at the University of Wisconsin one investigator has been studying stress in families with developmentally delayed children. This researcher has postulated periods of increased familial stress during important transition periods in the child's development and in the support services network (e.g., entry into school, placement outside the home).

In one study of parents' vs. professionals' accounts of parental adjustment to a mentally retarded child over the life cycle, professionals significantly underestimated the impact of transitions in later life. A subsequent study examined the stress levels experienced during the onset of adolescence and

around the onset of young adulthood. It was found that these two transition periods were indeed experienced as more stressful than were earlier periods. Research in this area is continuing in order to identify ways to ease the stress for the families during the most difficult periods of the retarded child's life. Other scientists in other MRRC's have also been studying how families with a retarded child experience and handle the stress associated with the child's condition.

Language and Communication Processes

Many mentally retarded children are first identified as such when they fail to develop normal language early in their lives. It is therefore of great importance to understand how young normal and retarded children learn to communicate. In the past, research on communication processes have led to the development of alternate language systems for handicapped individuals who did not have the capacity for normal speech.

One study at the MRRC at the University of Wisconsin investigated the communication skills of 130 mentally retarded individuals ranging in mental age from 8 months to 7 years. The purpose of the research was to examine how retarded children develop language. The researchers also focused on the degree to which the intellectual limitations of their study participants were related to language difficulties. The findings revealed delayed language comprehension in 17% of the sample and delays in syntax among almost half of the children. The researchers also analyzed the diversity among a subsample with regard to language development. Three patterns of language development could be identified: delays in both speech production and comprehension; delays in production only; and language functioning consistent with cognitive level. These three patterns are important to distinguish because they suggest very different approaches to educational planning and amelioration of the language difficulties among retarded children.

This same research team has made a major breakthrough in the methodology used to analyze language. One of the most powerful tools for identifying language disorders in handicapped individuals is the free speech sample: actual examples of children's storytelling and conversation that can be analyzed for developmental linguistic level and specific problems. This same tool is the most important one for determining therapy goals and evaluating their achievement. Ordinarily, such analysis of language transcripts takes a very long time and a great deal of effort. This severely limits the available resources. After four years, these researchers have perfected a computerized system for analyzing language samples. The technique, Systematic Analysis of Language Transcripts (SALT) can be carried out on a mainframe computer or on a micro-computer. This technique will make a valuable contribution to those studying normal language development as well as that of individuals with communication disorders.

Behavior in Residential and Community Settings

A large number of mentally retarded persons still reside in state operated institutions. One of the biggest problems in these facilities as well as in other institutional care settings is the rate of staff turnover. It is clear that the continuity of care in any service delivery system is an important ingredient in the provision of high quality care. Two investigators from the

Vanderbilt University MRRC have been studying the problem of staff turnover in a number of institutions for the mentally retarded. In one study they discovered that voluntary staff turnover increased during the first 8 to 16 weeks following initial appointment but leveled off thereafter. As a result of interviews with departing employees they learned that the major problem seemed to stem from a misunderstanding of what employees initially expected from their jobs and the actual demands of the jobs. In order to reduce this excessive high turnover rate, the researchers developed two interventions. In one case, a written job preview containing realistic and candid descriptions of the job characteristics was given to 149 prospective employees and withheld from 19 others. The second intervention consisted of presenting the same information as in the written previews as videotape presentations to 38 prospective employees and withholding the information from 82 others. In order to evaluate the effects of these interventions, attrition was monitored closely for 9 months following initial employment. Results indicated that both interventions produced some improvement in turnover rates. These results suggest that some but not all of the turnover in staff of institutions for retarded persons can be averted by providing realistic job previews to prospective basic-care staff. Research such as this study is essential in order to continue to improve the quality of life for retarded persons living in institutions.

STAFF ACTIVITIES

Forward Plan

In fiscal year 1983, the Branch initiated action to develop a forward plan to guide its research programming efforts. Sixteen committees were established to address research needs and opportunities in major areas of research activity relevant to mental retardation research. Each committee chairman was given autonomy to name the members of his or her committee. These committees will study problems in their assigned research areas and develop an initial report. These reports will be circulated between committees and consensus sought as to the research actions and initiatives which should have highest priority in Branch programming. Consumer (user) groups will also participate in the planning process as will concerned Federal agencies. A final report will be prepared and presented to the National Advisory Child Health and Human Development Council at its January, 1984 meeting. It is anticipated that this planning process will continue into subsequent years with revision and updating of the forward plan occurring each year.

Publications

Environments and Behavior, the 12th publication in the Mental Retardation Research Centers Series, was published this year. Learning and Cognition in the Mentally Retarded, a publication based upon a Branch supported conference on that subject at the George Peabody MRRC at Vanderbilt University, is currently in press and will be the 13th publication in the MRRC Series.

Conferences and Workshops

The Branch conducted two conferences in FY 1983. One, held in Bethesda in April 1983 addressed research issues concerned with the Fragile X syndrome. The second conference addressed the research issues concerned with retarded individuals

living in the family. This conference was held in joint sponsorship with the MRRC at the Univeresity of North Carolina at Chapel Hill in September.

Human Learning and Behavior Branch (HLB)

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PROGRAM ACTIVITIES

The program of the Human Learning and Behavior Branch (HLB) supports basic research and research training on behavioral development from the perinatal period to the beginning of adulthood. The primary focus of the Branch is to determine how the interaction of biological, psychological and socioenvironmental factors result in normative behavioral development and to identify those factors which interfere with such development. The program is divided into five major elements: (1) Biological Bases of Behavioral Development, (2) Learning and Cognitive Development, (3) Social and Affective Development, (4) Communicative Abilities; and (5) Behavioral Pediatrics.

Processes and behaviors specific to each stage of development are studied. These include studies of behavioral development in children born at biological risk for a variety of behavioral disabilities: learning problems, delayed or impaired speech and dyslexia.

Included in biological bases of behavioral development are studies of brain/behavior relationships, the biochemical, physiological and hormonal bases of behavior, sensory motor processes, and comparative animal behavior. This program element is divided into six topic areas: (a) Developmental Behavior Genetics; (b) Developmental Behavioral Endocrinology; (c) Developmental Behavioral Neurobiology; (d) Sensory and Psychomotor Development; (e) and Comparative Animal Models of Behavioral Development.

Learning and cognitive development includes research on basic learning mechanisms which are necessary for optimal behavioral development. In addition support is provided for studies of perception, cognition and memory. While the emphasis has been on infants, research applications are also encouraged for studies of children and adolescents.

Research in social and affective development is designed to gain an understanding of the basic behavioral, psychological and genetic mechanisms involved in normal social and emotional development. Included are studies of temperament, the family as a context for social and emotional development, prosocial behavior, development of self and body image in adolescents, and the influence of endocrines on emotional development. Also covered under this rubric are experimental studies which employ comparative animal models of social and affective development.

Communicative abilities supports research on the acquisition and development of speech, language, and reading ability in children. Included are studies of basic mechanisms, both physiological and behavioral, which underlie language and the learning of language by children. Special emphasis is given to research on the neural genetic and behavioral factors involved in dyslexia.

TABLE 4

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1983
HUMAN LEARNING AND BEHAVIOR BRANCH

Funds (in thousands)

Program Category	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	148	$14,961	129	$13,812	116	$9,800	8	$3,819	5	$194	18	$961	1	$187
Developmental Behavioral Biology	45	3,518	38	3,365	34	2,978	1	274	3	113	7	153	-	-
Human Learning, Cognition, Perception, Memory	38	3,724	30	2,972	25	1,760	3	1,131	2	81	8	752	-	-
Social and Affective Development	19	1,675	19	1,675	19	1,675	-	-	-	-	-	-	-	-
Human Communicative Processes	29	4,279	25	4,036	21	1,622	4	2,414	-	-	3	56	1	187
Behavioral Pediatrics	17	1,765	17	1,765	17	1,765	-	-	-	-	-	-	-	-

Note: The Minority Biomedical Support grant (S06) is included with the research projects.

Research in behavioral pediatrics focuses on applying principles of human learning to health and illness behaviors of children. In some cases adults significant in a child's environment are studied to gain an understanding of which behavioral mechanisms are instrumental in promotion of health and in prevention of disease. The goals of this element are (1) To link the basic findings in behavioral development with clinical concerns associated with the practice of pediatric medicine, (2) to determine how children learn about health and react to illness, (3) to examine the developing behaviors which promote health and well-being across the age span, (4) to study how lifestyles develop which encourage risk taking, and (5) to examine how these factors contribute to the etiology and onset of disease and impact upon the public health.

FINANCIAL SUPPORT

During the time covered by this report, funds for the five program elements amounted to $14.9 million. A total of 148 grants were supported. Approximately 80 percent of the grants (116) are regular research grants. The branch also supported 8 program projects and 18 grants for training. These latter grants support individual and institutional pre and postdoctoral training for research on behavioral development. Funds for training amounted to $961 thousand. A full breakdown of financial support is provided in Table 4.

RESEARCH HIGHLIGHTS

BIOLOGICAL BASES OF BEHAVIORAL DEVELOPMENT

A number of important findings have emerged during this past year in the fields of behavior genetics, developmental neurobiology and developmental behavioral endocrinology.

Behavior Genetics

Branch supported investigators using a chromosomal linkage approach have studied reading disability in nine families who had poor readers over three generations. As reported in Science, they found evidence in 8 of the 9 families studied that the reading disability was linked to chromosome 15. While family members may share a "reading" gene located on chromosome 15, the expression of their reading disability is very divergent. This divergence between a common biological basis and diverse phenotypic expression of reading disability has led these and other investigators to refine the behavioral measures of reading disability. When such measures are obtained, researchers should be able to more accurately specify the biological bases of reading difficulties.

Work on the interaction of genes and environment continues in the context of a study of visually guided behavior in birds. Two color preference strains (red and blue) have been bred in Japanese quail. The quail show genetic differences in post-imprinting tests to acquired color preferences. Preliminary data indicate that after the first four days of life, the "red" and "blue" strains show similar capacity to perceive color, code and store new elements of stimulus information. This work is a clear demonstration of

specific genetic influences on early color preference and behaviors acquired through visual discrimination.

Research supported by the Branch is also investigating genetic influences on aggressive behavior in mice. Two selectively bred strains evidenced differential onset of aggression. The "high" aggression strain showed the onset of male aggressive behavior at puberty. Males of the "low" aggressive strain exhibited aggression only during the post puberty period. Females of the two strains did not segregate for aggression until after they passed through the age of reproductive fertility. The "low" aggression females, similar to the males of the strain, demonstrated a delayed onset of aggression.

Developmental Neurobiology

In one of the most basic studies supported by the Branch, a researcher is studying the neural basis of learning in mollusks. The mollusk, Hermissenda, exhibits associative learning which involves the suppression of visually guided locomotor behavior. The aspect of behavior that can be conditioned is the amount of time that the animal spends in bright light. Results indicate that conditioned animals spend less time in bright light. This change from normal behavior can be predicted by knowing the neural activity of light adapted B-photoreceptors following conditioning. These findings provide important evidence of the way sensory neurons and motor neurons interact to generate learning in simple organisms.

Brain sexual dimorphism continues to be investigated by Branch supported scientists. Two recent developments are worthy of mention. In a recently published article in Science magazine it was reported that male macaque monkeys have more dendritic material in the preoptic area of their brain than females of the same species. This is the first report of sex differences in fine structural organization of the primate brain.

In a related development, researchers from the same laboratory studied sex differences in rodent brains. They found that the visual cortex differed between male and female rats. In layer III, pyramidal cells showed more plasticity in males than females. In layer IV of visual cortext the trend by gender continued but was less pronounced than in layer III. No differences were found between sexes in layer V. Such anatomical differences are quite interesting but await experiments to elucidate their functional significance.

Developmental Behavioral Endocrinology

A major finding by a Branch supported scientist documents maternal coordination of the fetal biological clock of rats. As reported in Science magazine, the results indicate the existence of an entrainable circadian clock in the suprachiasmic nuclei during fetal development. Additional evidence supports the view that the maternal circadian system coordinates the phase of the fetal clock to environmental lighting conditions.

Research on hormonal bases of aggression in mice suggests independent androgen and estrogen sensitive aggression activating systems. Using gonadectomized males from three strains of mice exposed to natural or synthetic androgens and estrogens the investigator differentiated two systems. He found that the androgen sensitive system is apparently present in the three strains studied;

however, one strain (CD-1) is insensitive to the aggression promoting properties of estrogen.

The research reported above highlights the relevance of hormones in the development of important species specific behavior.

LEARNING AND COGNITIVE DEVELOPMENT

This element of the Branch program focuses upon comparative animal models of early learning, perception in infants, and cognitive development in children and adolescents.

Early Learning in Animals

Animal models are important, for they provide an approach to study learning mechanisms under prospective, highly controlled conditions. Results can suggest hypotheses concerning the underpinnings of human learning.

Two Branch supported researchers are studying learning in utero. One scientist who is investigating imprinting in mallard ducklings has found that the embryo must experience the normal variation of embryonic auditory stimulation if their auditory perceptual specificity is to be normal at the usual time after hatching. These results indicate the need for detailed information about sensory stimulation during development. Such information is necessary to interpret the results of early manipulation of environmental stimulation and critical period.

Another Branch supported scientist is investigating learning in utero using an odor aversion procedure with neonatal rat pups. A solution of lithium chloride and apple juice was injected into rat pups while they were still in utero. Ten days post-partum the rat pups traverse a runway for an opportunity to suckle from an anesthetized dam. When running speed stabilized, the odor of apple juice was introduced into the running task. Those pups which had been conditioned prenatally decreased running speed over trials. Some even failed to traverse the runway. The diminished response to the odor of apple juice demonstrates that in utero conditioning can occur with just one pairing of an aversive stimulus (lithium) and a neutral stimulus (apple juice).

Two other studies are investigating very early learning in rat pups. One researcher found that excitation or activation is essential for early learning. Such activation may be dependent upon deprivation of specific forms of environmental stimulation. When rat pups are fed intragastrically from birth and the surrogate mother (a towel) is removed, the pups can no longer mouth and nuzzle the towel. This form of sensory deprivation could change the reinforcing properties of oral stimuli as the rat pups develop.

In another study in which twelve day old rat pups were observed, the researcher noted the appearance of chin scraping and paw treading to the taste of quinine, strong saline, and citric acid. These observations suggest the maturation of an aversive response system. The responses which occurred to aversive tastes could be elicited by formerly neutral cues after pairing with citric acid. These results point to the high likelihood of being able to study conditioned responding at a time in development when the response system itself is undergoing rapid change.

Visual Perception in Infants, Children, and Adolescents

A number of studies continue to assess the capacity of newborns and infants for visual perception. Branch supported researchers have found that binocular fixation can be observed in infants after birth and can become a reliable response to moving targets by two months of age. Another study has shown that binocular depth cues are functional by three months of age.

A Branch supported researcher reported on a comparison of 6 week-old and 12 week-old babies regarding their capacity for visual feature detection. Such detection is poor at 6 weeks but nearly as good as adults by 36 weeks. By contrast, neither 6 week-olds nor 12 week-olds show capacity for light adaptation as effectively as adults do.

Work focused upon the infant's perception of objects in the environment reveals that 6 month olds demonstrate a preference for the number of objects in a visual array which corresponds to the number of drum beats (2 or 3) that they heard. These results suggest that babies at this age have a rudimentary concept of number.

Branch supported scientists have been studying the infants' perception of emotion. They found that 7 month old infants can respond to the expressive characteristics of a face not just its structural aspects. One surprising result, reported in Science magazine, is that 2 week olds are able to imitate facial expressions of adults. Researchers previously thought that such imitative learning appeared much later in development.

In a study of perceptual abilities in adolescent girls, face encoding improves markedly between the ages of 10-12 years but declines at age 14. By 16 years facial encoding by females surpasses the capacity seen at 12 years. For boys, face encoding improves steadily from 10-14 years, then worsens between the ages of 14-16. The capacity is considerably worse for boys at 16 than girls of the same age.

Cognitive Development

One Branch supported researcher has studied the response by 6 and 8 year old children to ambiguous instructions. Six year olds exhibit less puzzlement over inconsistent instructions. They may not even know that the instructions are ambiguous. Another project is focusing upon recognition memory in 3 year olds. The research results indicate that memory is facilitated when tasks are completed during an interaction with the child's mother. However, the results do not hold for children who are 5 years old.

The understanding of scientific concepts (numbers, time, proportionately, and living versus non-living) is being studied in subjects from childhood through adolescence. Young children appear to follow a series of discrete rules that ultimately lead to mastery of concepts. Four to five year olds for example, when given a simple addition problem such as 1 + 1, first try to retrieve (recall) the correct answer. If incorrect, they next try to generate a more elaborate representation of the problem, perhaps by putting up their fingers. The more difficult the problem, the more likely they are to use such overt strategies as counting on their fingers.

SOCIAL AND AFFECTIVE DEVELOPMENT

The Branch continues to support research on social and affective development. During the past year a number of studies have begun in the areas of adolescence and the family.

Social Interaction in Children

Two Branch supported scientists are studying the roots of prosocial behavior in children. One grantee found that 18-30 month-old toddlers show spontaneous helping and such behaviors appear to be goal directed. A second study involving 16-32 month old children showed that peer imitation of social acts can foster successful social interactions. Another grantee is investigating correlations between the social interaction skills and cognitive/social reasoning abilities in 2-5 year olds.

Adolescence

The 1982 NICHD announcement on adolescence research has stimulated considerable interest in the scientific community. The Branch now supports 15 studies on adolescent development. Three newly funded grants focus respectively upon: (1) The impact of menarche on psychological functioning; (2) The role of adolescent social networks in behavioral development; and (3) The network supports used by young adults during transition to employment, marriage and parenthood.

Preliminary results from the first study suggest that the age of menarche of white middle class girls is lower than expected on the basis of published norms. It is not yet clear whether the findings are related only to the sample being studied or are indicative of a general trend. Results from the second study found differences in the social networks of adolescent boys and girls. Males felt closest to females, whereas females did not show a preference for gender along the dimension of closeness. Both males and females indicated that older persons and parents were the ones to whom they felt closest. The third study is concerned with networks used by young adults in their transition to adulthood. The findings, as expected, confirm the observation that educational attainment increases the likelihood of socioeconomic success. The data, when totally collected, should allow the construction of a causal model of the transition process. This model should help identify the important variables necessary for successful transition and determine how the variables interact and respond to gender influences.

The Family

The family continues to be a major focus for studying the context in which human behavior develops. Branch supported research is investigating both intrafamilial and extrafamilial processes.

Two studies now underway are investigating the characteristics of family members and family interaction patterns prior to the birth of a child through infancy. Preliminary results from one study show a significant, positive relationship between the degree to which a husband and wife interact and the degree to which the father and infant interact. Results from the second project have demonstrated relationships between maternal confidence about

motherhood and ego strength during pregnancy and children's IQ at age three. Those mothers high on both measures had children with the highest IQ.

Family constellation variables (birth order, family size, and gender) are important determinants of behavioral development. In young children (33 months) social interaction depends on their birth position within the family. Only children were the most socially active, the oldest child next most socially active, and the youngest child the least active.

Two Branch supported scientists have been investigating family constellation variables in combination. In one study, the researcher found that SES and minority status were generally more important determinants of school achievement and personality than birth order and family size. A second study of sibling and parent relationships found that gender and birth order are not good predictors of the quality of a relationship between family members (i.e., feelings of closeness, helpfulness, affection, nurturance or admiration).

Previously, the Branch has supported research on extrafamilial influences such as race, ethnicity, location (urban/rural), and mobility on social and cognitive development in children. Currently supported research is investigating how parents allocate resources to their children according to the children's abilities and constellation status. Another project is studying, in the context of a cross cultural approach, how conscience, guilt, and morality develop in the family.

COMMUNICATIVE ABILITIES

This aspect of the Branch program focuses upon biological, behavioral and psychological bases of speech, language, and reading development. Work includes research utilizing animals and children to study the development of simple and complex communication behaviors.

Comparative Animal Models

In recent years attention has focused upon the developing brain of birds as a model for the acquisition of communication behaviors (species specific song). The Branch supports both laboratory and field studies designed to elucidate biological and environmental factors involved in song acquisition. One such study, which investigated territorial songs of sparrows, found that male birds usually sing like the territory holders and not their fathers. This finding demonstrates that song learning is partially dependent upon environmental factors.

Another research project is studying language acquisition in chimpanzees. The chimpanzees, who have been highly trained to use language symbols, were initially required to remember four types of food which were hidden simultaneously. Next they had to request specific items. Chimpanzees correctly recalled the required information on 66-75% of the trials. This result indicates that apes are capable of recall in non-spatial tasks, an ability necessary for language. The scientists conducting this animal language project have developed a method for presenting visual symbols differentially to the two hemispheres of the chimpanzees. This approach should allow questions to be formulated concerning language acquisition and brain laterality in apes. Because language capacity is left hemisphere dominant in man, this animal model

may provide a significant new opportunity for biobehavioral studies of language acquisition.

Research in Reading

The Branch supports a number of studies designed to determine how children learn to read and to examine factors which interfere with the acquisition of this capability. A number of important advances have been made on characterizing and measuring reading deficits.

One scientist found that children who have difficulty reading have slower reaction times to visual stimuli when compared to normal controls. Another researcher found that 3rd and 5th grade disabled readers have difficulty reading non content words (i.e., this, that, and the) compared to normal controls. A preliminary analysis of data from this same laboratory indicates that evoked potentials to content and non content words are significantly different in disabled readers.

Disabled readers have been found to differ from controls in their use of perceptual units. A Branch supported scientist found that in contrast to able readers those with reading difficulties do not use letter clusters to analyze reading materials. When two or more letters are presented to disabled readers, they do not integrate the information on item structure, order, or position of the letters. In addition, reading disabled children are slower to use different cognitive processes when reading. One researcher found that in simple pattern recognition of visual phonemic transfer of information, disabled readers have fewer evoked responses from the right brain hemisphere than do normal controls. These data suggest that disabled readers may use different neural processes than normal readers.

A five year longitudinal study of disabled readers found that when verbal IQ differences are partialled out, such disabled readers do not differ from normal controls on performance or full scale IQ. While both normals and disabled readers show similar rates of improvement in reading abilities, the disabled showed almost no improvement in symbol processing.

Advances have been made in methods for more accurately and comprehensively measuring eye movements of children while they are reading. An investigation of the eye movements of disabled readers indicates that disabled readers have longer fixation durations, shorter saccades, and a higher percent of regressive eye movements. In a reading aloud condition, phonologically impaired disabled readers had a high frequency of regressive eye movements. In a silent reading condition these regressions decreased. This finding may have important implications for testing and teaching disabled readers. A recently awarded grant will focus upon the development of eye movement patterns in children (1st, 3rd & 5th grade) as they learn to read. This work should provide developmental standards and provide the necessary information for early detection of reading disability.

BEHAVIORAL PEDIATRICS

Behavioral pediatrics is the newest element of the Branch program. During this past year a number of interesting findings of relevance to pediatricians have emerged.

Health Behavior

In the area of health promotion for example Branch supported investigators have been studying how to teach concepts of safety and nutrition to children 2-4 years of age and to their parents. The results to date indicate that children in the experimental group initiated and practiced health and safety behaviors more often than the controls. They were more likely to practice these behaviors spontaneously.

Of interest is the way that children and parents comply with medical regimens prescribed by pediatricians. One NICHD grantee is comparing the mother's use of non-prescription drugs and home remedies for her child's illnesses and her own health beliefs and attitudes with the pediatric clinic records on the child's health and medical prescriptions. Preliminary findings indicate that income and educational level largely determine the kind of medical measures used by mothers. The number of over-the-counter medications that mothers keep on hand increases with SES level, from an average of 4.73 in the clinic serving lower-income families to an average of 8.96 in the clinic of a more prosperous community.

Illness Behavior

Currently, the Branch supports two studies of chronic illness in children and its impact on the family. One is assessing the psychological adjustment of the family members and disabled children (6-18 years) (e.g., cystic fibrosis, cerebral palsy, myelodysplasia) with siblings of the afflicted children and those from randomly-selected families in the same community. Findings indicate that children with cystic fibrosis are not at an increased risk for psychopathology. However, children in the other diagnostic groups show a substantial increase in cognitive deficit and social isolation. Also, siblings of disabled children evidence an increase in aggression and anxiety compared to controls. The second study is evaluating methods to develop effective psychological counseling for parents and diabetic children. The outcome measures used to assess success are both behavioral (self-report measures) and biological (hemoglobin $A1_c$).

Risk Taking

Under this heading are grouped studies designed to further our understanding of behaviors which are harmful to health, such as use of cigarettes, overeating, and accident-proneness. This category also includes studies of the development of children born to women who smoked or ingested harmful substances during their pregnancy.

Two important topics under study are the role of personal and social influences upon the onset of smoking in teenagers, and the impact of maternal smoking on the biobehavioral development of the fetus and child.

At a recent national meeting, Branch staff organized a symposium "Becoming A Cigarette Smoker: The Acquisition Process in Youth." Institute supported scientists have pioneered the development and use of biological markers (saliva thiocyanate, carbon monoxide, and plasma cotinine) to assess smoking status. More recently, the research focus is upon new methods for quantitatively assessing response topography (puff frequency, puff duration, and puff volume).

Such measures will allow researchers to better estimate nicotine exposure levels in children who smoke. Findings of interest, which emerged from the symposium, indicated that junior high students' measures of intention to smoke were the best predictor of smoking one year later. Further, adolescents who are at risk to begin smoking grossly overestimate the actual prevalence of smoking among adults and teenagers.

Biobehavioral research related to smoking during pregnancy is receiving increased attention from the Institute. In a forthcoming article in the Journal of the American Medical Association, a Branch supported researcher presents findings on a prospective clinical study involving 935 pregnant smokers who were randomly assigned to treatment (a smoking cessation program) and to a control group. Results indicate that cessation of smoking as late as the eighth month of pregnancy reduces fetal growth retardation. At birth, the treatment group infants showed a statistically significant increase in birth weight and body length over that of the control group. This finding was unrelated to gestational age.

Another important study supported by the Branch is following 17,000 British children born to smoking and non-smoking mothers. At the five year follow-up, children born to mothers who smoked during pregnancy still exhibited significant differences from controls in head circumference and height. Also, after controlling for social and behavioral characteristics of mothers studied, a dose-dependent relationship was found among children of smokers regarding their comportment. They were more hyperactive, antisocial and exhibited increased enuresis. This latter result was limited to children of mothers who smoked more than 15 cigarettes per day during pregnancy.

Neonatal Behavior

Grouped in this category are basic research findings which have implications for clinical practice of pediatrics. Three studies are now under way investigating neonatal pain, measurement of hearing in one-day old babies, and development of motor behavior.

The measurement of pain in neonates was assessed by observing behavior and adrenocortical response in male babies who were circumsized. Non-nutritive sucking on a pacifier soothed babies (they cried 35% less than controls). However, the soothed babies' adrenocortical response to tissue damage was not altered by access to the pacifier. The study is important because it has implications for procedures routinely practiced without anesthetics in the NICU.

A Branch supported researcher has found that the glabella (eye blink) reflex can be augmented by presenting an auditory stimulus concurrently with a tap to the head. The reflex can be inhibited by presenting an auditory stimulus 200 ms prior to the tap. By using tones at different intensities and frequencies to either augment or inhibit the reflex, the scientist has been able to test the hearing of sleeping babies in the neonatal nursery. He accomplishes this by measuring the baby's eyeblink response to combinations of tones and taps to the head. His findings have important implications for developing early screening tests for hearing deficits.

Another Branch supported scientist is investigating the normal motor development of babies 2 weeks - 20 weeks of age using kinematic and EMG measures of spontaneous movement. The results to date challenge the traditional view that limb movements by very young infants are random and disorganized. The researcher found flexor dominance in movement; synergies of hip, knee, and ankle joints; and non-random temporal durations of the movement phases of the kick. As infants mature they increasingly demonstrate "liberation" of one joint (usually the hip) from the synergy of motion among hip, knee, and ankle. The extension movement becomes more a result of phasic activation and less a passive phenomenon. The results are important for they can provide a baseline against which to measure delayed motor development.

STAFF ACTIVITIES

The HLB Branch sponsored three conferences at the end of FY 83. These were: (A) Developmental Behavioral Pharmacology (August 21-14, 1983); (B) Children's Health Behavior Pediatrics (September 11-14, 1983); and (C) Genetics and Learning (September 20-23, 1983).

Members of the HLB staff have been actively involved in organizing scientific symposium and publishing papers and monographs related to the Branch's scientific program. Dr. David Gray co-authored a paper with Dr. Sumner Yaffe entitled: Prenatal Drugs and Learning Disabilities. It was presented at the Association for Children with Learning Disabilities International Meeting in Washington, D.C. in February 1983.

Dr. Josephine Arasteh organized and chaired a symposium entitled, Becoming a Cigarette Smoker: The Acquisition Process in Youth at the annual meeting of the American Psychological Association in Anaheim, California in August 1983.

Dr. Phyllis Berman presented a paper entitled: Children's Nurturance to Younger Children: Age Sex and Situation at the Society for Research in Child Development meeting in Detroit, Michigan, April 1983. She also organized a symposium on Sex Role Research and Its Contribution to Theories of Development. It was presented at a meeting of the International Society for the Study of Behavioral Development, Munich, Germany, August 1983.

Dr. Norman Krasnegor organized and chaired a symposium on Behavioral Pediatrics at the annual meeting of the Society for Behavioral Medicine, Baltimore, Maryland, March 1983. He organized and chaired a symposium on Compliance Behavior to Medical Regimes in Children at the Annual meeting of the American Psychological in Anaheim, California in August 1983. Dr. Krasnegor is co-editing a book with Dr. Gilbert Gottlieb, University of North Carolina, Greensboro, on the Measurement of Audition and Vision During the First Year of Life. The monograph which is to be published by Ablex Publishing Corporation will be available in the spring of 1984.

Three new staff have been added to the Branch: Mrs. Etta Kidwell, Branch Secretary; Ms. Arlette Williams, Clerk-Typist; and Mr. Gary Carter, Program Assistant to Dr. Gray.

* U.S. GOVERNMENT PRINTING OFFICE: 1984 421-132:5299

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